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CIRRHOSIS OF THE LIVER. FIVE DIFFERENT TYPES OF LESIONS FROM WHICH IT MAY ARISE.[1]

By F. B. Mallory, M. D.

(From the Pathological Laboratory of the Boston City Hospital.)

Introduction.—In some organs the late stages of certain lesions have received more attention than the beginnings of these lesions. The emphasis has been placed on the wrong end of the process. This statement is particularly true of the inflammatory changes in the liver and in the central nervous system.

Now, in order to understand a pathological process, it is necessary to find and study its beginning and to trace its biological development. It is with this view in mind that I shall present to you to-night a study of five different types of early lesions of the liver so that you may see for yourselves how the late stages of these lesions resulting in sclerosis would all be classed under the term cirrhosis. It will enable you better to appreciate what very different kinds of pathological processes the term covers.

I shall not present these different types of lesions in the order of their relative frequency and importance, but in such sequence as will throw most light on certain features common to them all, especially the changes in the connective tissue stroma.

To the clinician the term cirrhosis usually means a chronic, progressive, destructive lesion of the liver combined with reparative activity and contraction on the part of the connective tissue. This contraction of the connective tissue may lead to obstruction of bile ducts, causing more or less jaundice, and to interference with the flow of blood through the blood vessels resulting in portal congestion and ascites.

The pathologist uses the term cirrhosis in a broader sense. He applies it to all sclerosed conditions of the liver, whether progressive or not, in which destruction of liver cells is associated with real or apparent increase of connective tissue. It is from the pathologists' point of view that I approach the subject.

I shall have to refer first to three pathological conditions which may complicate some of the changes terminating in sclerosis.

The first of these, fatty infiltration, is common but of little significance except that under certain conditions the fat present in the cells seems to serve as nutrition and thus aids to protect to some extent the liver cells containing it from undergoing necrosis as readily as surrounding cells containing none.

The second is chronic passive congestion. When this condition is uncomplicated it seems not to cause disappearance of the liver cells around the hepatic vein in the lobule as is generally taught. The cells disappear as the result of a toxic necrosis complicated with hemorrhage. If, as is usually the

[1] Read before the Johns Hopkins Hospital Medical Society, Nov. 7, 1910.

case, the necrosis is recent, due to a terminal infection, it is easy to demonstrate the necrotic liver cells in the midst of the red blood corpuscles filling the trabecular spaces. If the necrosis is of longer standing the necrotic cells will have partially or entirely disappeared under the solvent action of polynuclear and endothelial[2] leucocytes. The trabecular spaces, dilated and filled with blood, are readily mistaken for distended sinusoids. As a matter of fact the sinusoids are usually more or less compressed as the result of the hemorrhage. In time the hemorrhage disappears and the sinusoids again dilate. Owing to the condition of congestion the liver cells do not regenerate. Consequently, in time, the trabecular spaces shrink and the connective tissue contracts and thickens, although it does not increase in amount, and the liver by its consistence may suggest a mild uniform type of sclerosis.

The third and most important pathological condition to which I must refer is general bile stasis due usually to obstruction of the common bile duct by a calculus or by a tumor. This condition leads to marked dilatation of the bile capillaries around the hepatic vein, to rupture of them, and to the escape of masses of inspissated bile into the lymph space between the liver cells and the wall of the sinusoid. Here the bile is incorporated by endothelial leucocytes and gradually dissolved. After solution it seems to pass, perhaps by osmosis, directly into the blood stream, not along the lymph channels to the thoracic duct. Apparently uncomplicated bile stasis does not result in any sclerotic process around the hepatic veins where the chief lesion is located and it certainly does not around the portal vessels.

I. Toxic Cirrhosis.

A fairly common affection of the liver is necrosis of the cells around the hepatic vein, the so-called central necrosis, due to toxins in the circulation. It is a frequent terminal lesion. Occasionally the necrosis is limited more or less definitely to the midzonal region. This type of lesion may be slight, or very extensive involving nearly all the cells in a lobule. It is usually quite uniformly distributed throughout the whole liver. In the milder degrees of necrosis the liver cells are quickly invaded by polymorphonuclear or endothelial leucocytes (Fig. 1) or by both, dissolved, and removed. If the patient survives, the liver cells usually regenerate and the liver lobules are restored to their normal appearance. Sometimes, however, the liver cells do not regenerate. Then the walls of the sinusoids collapse, the lobules shrink, and the connective tissue around the hepatic veins appears thickened, just as may happen in connection with chronic passive congestion. Experimentally it has been shown that this form of lesion may be produced by chloroform narcosis and that regeneration will quickly take place.

Occasionally this type of necrosis is very extensive so that in some lobules every liver cell is killed. If the patient survives, the necrotic liver cells are invaded and so quickly removed by the action of leucocytes (Figs. 2 and 3) that in five or six days the liver will diminish in weight from 1500 grams to 600 or 500 grams or even less. The liver will be perfectly uniformly lessened in size, and flabby to the touch. This is the early stage of so-called acute yellow and red atrophy of the liver. If the patient still survives, active regeneration takes place, the liver cells giving rise to new liver cells, bile duct epithelium producing bile duct epithelium. As a result of this active regeneration those parts of the liver where liver cells persist rapidly enlarge and the lobules assume more or less completely their former shape, or perhaps undergo compensatory hypertrophy. These are the yellow bile-stained areas of acute yellow atrophy of several weeks' duration. In those parts of the liver where all the liver cells were killed, the bile ducts (Figs. 4 and 5) grow a third or half the way towards the hepatic vein and then stop. They do not produce liver cells. The lobules are much diminished in size, the leucocytes disappear from the trabecular spaces, the sinusoids are dilated. These are the red parts of a case of acute yellow atrophy of two to several weeks' standing.

This type of lesion teaches two things that are of importance in considering the other types of lesions which result in cirrhosis. First, that simple necrosis of liver cells without injury to blood vessels and connective tissue stroma, does not result in proliferation of connective tissue. The connective tissue which is there shrinks together and thickens, leading to an apparent but not real increase of it. Second, that liver cells regenerate only from liver cells. The bile ducts lengthen owing to proliferation of bile epithelium but they cannot form liver cells.

Various degrees of this series of lesions known under three different names, central necrosis, acute yellow and red atrophy, and cirrhosis, are not, I believe, so infrequent as is generally supposed. It ought to be possible to recognize the resulting type of cirrhosis long after the acute lesion is over even without a clinical history to help. Two points are of diagnostic value: the very irregular distribution of the connective tissue as seen on gross examination: and the preservation of the shape of the lobules, much shrunken, in the sclerosed parts. Whether or not continued contraction of the connective tissue may in time lead to obstruction of bile ducts and blood vessels resulting in jaundice and ascites, I am at present unable to say.

It is of interest that this type of cirrhosis is of acute origin; therein it differs from the four other varieties which are all of a more or less chronic nature.

[2] The endothelial leucocyte arises by proliferation and desquamation of endothelial cells lining blood and lymph vessels. It emigrates from vessels like the other leucocytes, multiplies by mitosis in the vessels and tissues like the lymphocyte, and possesses one especially distinguishing property, that of being under certain circumstances very phagocytic for the other leucocytes as well as being able to incorporate red blood corpuscles, various microorganisms, and foreign bodies of all sorts. This leucocyte is known by various names, the large mononuclear of the blood, the nongranular leucocyte, the macrophage, etc. Its origin is best studied in the early lesions of typhoid fever, in very young miliary tubercles, and experimentally by the subcutaneous injection of agar.

II. Infectious Cirrhosis.

The second type of cirrhosis I shall term infectious cirrhosis because it is due to the presence of bacteria in the lesions. In my experience it is comparatively rare. Bacteria may and do gain access to the liver by direct continuity and through the hepatic artery, the portal vein, and the bile ducts. It is only of infection through the bile ducts that I shall speak here, as this seems to be the only form of bacterial infection which leads to a dictinct form of cirrhosis.

Infection through the bile ducts, when there is bile stasis from gall stone or other obstruction, not infrequently leads to infection with various bacteria and to necrosis (Fig. 9), abscess-formation, and death. A rarer form of invasion sometimes takes place along apparently normal bile ducts and leads to a very characteristic type of cirrhosis. It is to this variety of infection that I wish to call your attention.

My experience of the early stages of the process is limited to two livers which agree very closely in their gross and microscopic appearances although the infection is of longer duration in one than in the other. Both were from children, a girl[3] of twelve and a boy[4] of three. At post mortem examination the livers were two to three times the normal size and much increased in consistence. The surface and cut section were smooth. Clinically jaundice and enlargement of the liver were prominent symptoms.

What the infecting organism is I do not know as infection was not suspected and no cultures were taken. The bacteria present in the acutest lesions in the girl are slender bacilli (Fig. 7). In many ways the lesions in the liver may be said to correspond to the chronic process produced in the kidney by the colon bacillus.

Infection is spread chiefly through the bile ducts but the organisms have also invaded the surrounding connective tissue and are spreading through it. The pathological changes are confined almost entirely to the region around the portal vessels and are extending quite uniformly toward the hepatic vein of each lobule. The lesion is by nature chronic. It is active and spreading in many places; quiescent and healing in others.

The bile ducts (Fig. 8) frequently show more or less dilatation and in some places are filled with polymorphonuclear leucocytes (Fig. 10), in other places with endothelial leucocytes (Fig. 8). Here and there where the process is active the bile duct epithelium is necrotic or gone and the exudation is spreading into the surrounding tissue (Fig. 10). Here the bacteria lead to necrosis of the liver cells, of the blood vessel endothelium and of the fibroblasts, and to an acute inflammatory exudate consisting of polymorphonuclear leucocytes and fibrin. Where the process is less active and the bacteria have died out the exudation consists chiefly of endothelial leucocytes many of which are phagocytic and contain fragments of cells. Mitotic figures in endothelial leucocytes are found occasionally. Lymphocytes are present in relatively small numbers. The lymphatics (Fig. 6) in the capsule of the liver are in places distended and filled with endothelial leucocytes and a little fibrin.

Proliferative activity on the part of the fibroblasts is well marked and evidently follows the direct injury done the connective tissue cells by the toxins from the bacteria; in other words it is simple regeneration.

As a result of the exudation around the portal vessels, of the encroachment of the process on the liver cells, and of the proliferative activity on the part of the fibroblasts, the portal tissues show up as broad bands running very regularly between the lobules of the liver cells (Fig. 11).

In those parts of the liver where the lesion is older and the exudation is less active the bile ducts are more or less dilated and often appear considerably increased in number as though a diffuse bile duct adenoma were present. This appearance is probably due to contraction following marked dilatation and stretching of the ducts when the lesion was more acute. In those parts of the liver where complete repair has taken place this same apparent increase in the size and number of the bile ducts in the midst of abundant scar tissue is still noticeable, at least in the early cases.

In many places the inflammatory exudation in the smaller bile ducts has led to occlusion of them and to obstruction to the outflow of bile which appears in the ducts and bile capillaries above the point of obstruction in the form of yellowish green inspissated masses. The obstruction is focal only, not general and complete; therefore, the resulting jaundice is not intense.

The characteristics of this type of cirrhosis, while the infectious process is still active, are apparently the following:

The lesion spreads very uniformly from the portal vessels toward the hepatic veins, rarely cutting into a lobule. As a result the true lobular arrangement is more or less perfectly preserved. The bile ducts are often dilated and tortuous, so that they appear increased in number. The injury done the fibroblasts leads to active regeneration on their part and to the production of abundant connective tissue. As the result of the extensive inflammatory exudation and of the regeneration of the connective tissue the liver is much increased in size. The surface and cut section are comparatively smooth, perhaps owing to the even distribution of the inflammatory process.

Two cases of congenital jaundice with a uniformly distributed cirrhotic process and obliteration of the common bile duct show microscopically a marked increase of connective tissue around the portal vessels and are undoubtedly due to intrauterine infection extending along the bile ducts (Fig. 12).

III. Pigment Cirrhosis.

A third form of cirrhosis which deserves mention is that known as pigment cirrhosis, occurring in cases of hemochromatosis. It appears to be due entirely to mechanical causes. Endothelial leucocytes filled with blood pigment collect often in great numbers in the lymphatic spaces and vessels.

[3] Autopsy by Dr. O. R. Mabee.
[4] Autopsy by Dr. H. A. Christian.

of the liver, chiefly around the portal vessels (Figs. 13 and 14) but to some extent around the hepatic vein and irregularly throughout the lobule between the liver cells and the walls of the sinusoids. Whether they emigrate from the sinusoids after becoming filled with pigment, or absorb it like the liver cells and bile epithelium from the hemoglobin dissolved in the serum and lymph cannot be determined. But after they are filled with pigment they unquestionably are able to migrate. Wherever they collect in numbers they seem to injure the connective tissue mechanically by stretching it. In consequence there is a certain amount of regeneration on the part of the fibroblasts so that more or less sclerosis (Fig. 14) is produced.[5]

A similar increase of connective tissue is caused in the same way under similar conditions in the pancreas, adrenals, and lymph nodes. In time more or less of the pigment is dissolved by the action of the endothelial leucocytes, which then disappear, leaving the connective tissue behind as the only remains of the process.

This lesion, like infectious cirrhosis, may result in the acute stage in a large, smooth liver weighing in one instance, from a woman, 2500 grams. The primary injury seems to be done to the connective tissue. By contraction of this connective tissue later, more or less injury is probably caused to the liver cells.

The sclerosis which occurs in the liver and other organs in the pathological condition known as hemochromatosis is perfectly analogous to that which takes place in the lungs and peribronchial lymph nodes as the result of the inhalation of large amounts of carbon. Endothelial leucocytes carry much of the pigment into the walls of the alveoli and from there to the lymph spaces and vessels around the bronchi and larger blood vessels. Many of the cells remain packed in these situations and lead to considerable increase of the connective tissue.

Many of the cells in the lymphatics are carried to the peribronchial lymph nodes. At first they lie free in the lymph sinuses but soon migrate into the parenchyma when they lead to increase of connective tissue and secondarily to gradual disappearance of the lymphocytes. Some of the endothelial leucocytes filled with pigment migrate into the capsule of the lymph node and into the adjoining fat tissue.

This type of cirrhosis is characterized by pigmentation, by a very uniformly distributed increase of connective tissue, and by a smooth surface of the liver, externally and on section. It may attain a fairly large size. The increase of the connective tissue seems to be due to mechanical causes only.

IV. Syphilitic Cirrhosis.

Syphilitic infection of the liver is usually divided into two types, the congenital and the acquired. In the congenital type a diffuse lesion predominates, in the acquired a focal lesion; but the two types of lesions are often combined in the congenital form and may coexist to some extent in the acquired.

[5] See Cirrhosis Hepatis Anthracotica, by W. H. Welch, Johns Hopkins Bulletin, 1891, vol. II, 32, where I should interpret the origin of the sclerosis in the same way.

The primary, essential lesion produced by the treponema pallidum is best studied in chancres removed before necrosis has begun and in the liver and other organs of cases of congenital syphilis. The so-called tertiary lesions would probably be equally serviceable for study if they could more often be obtained before the stage of necrosis.

In studying syphilitic lesions it is necessary at our present stage of technical development, to prepare two parallel series of sections, the one stained by Levaditi's method after fixation in formaldehyde so as to demonstrate the causative agent, the other by various methods after fixation in Zenker's fluid to show the tissue reaction. When this is done it is found that the treponemata, present often in great numbers in the primary as well as in the congenital lesions, are situated in the minute lymph spaces between the cells and especially between the fibrils. They occur most numerously in the connective tissue between the collagen fibrils everywhere within the area invaded including that in the intima of arteries and veins. The injurious action of the organisms is exerted chiefly if not exclusively on the fibroblasts which are thereby stimulated to active regeneration, as a result of which much fibrous tissue is produced. This leads in part at least to the hardness of the primary lesion and to the sclerosis of the liver and other organs in congenital cases.

In the congenital lesions the tissue reaction often does not go beyond this stage. In the primary and tertiary lesions, however, the reaction is more intense. As a result there is added to this proliferation of fibroblasts an inflammatory infiltration consisting chiefly of lymphocytes including plasma cells, often also of numerous eosinophiles. Under certain conditions giant cells are formed from the endothelium lining the smaller blood vessels and also perhaps the lymph vessels. These giant cells may occur in chancres, in gummata, and especially in tertiary lesions of the skin. They are due to the presence of the treponemata within the blood and lymph vessels and to their action on the endothelial cells. The resulting giant cells often contain treponemata in large numbers.

The same lesion of proliferation of fibroblasts taking place in the walls of veins and arteries, especially in the intima, leads to narrowing and more or less complete occlusion of many of the smaller vessels. The areas thus deprived of nutrition gradually undergo necrosis (gumma formation) which results in an active inflammatory exudate of serum and of endothelial leucocytes (caseation); less often of polymorphonuclear leucocytes (suppuration). With the occurrence of the necrosis and of the acute inflammatory exudate the treponemata as a rule rapidly disappear from the lesion and the area affected tends in time to heal, owing to a local immunity being apparently produced by the leucocytosis. In this respect the focal lesions in syphilis differ materially from those in tuberculosis which tend to spread indefinitely.

Reverting now to the liver we find that in congenital syphilis the treponemata injure primarily the connective tissue cells, especially those lying between the liver cells and the walls of the sinusoids. As the result of the active and con-

tinued proliferation of the fibroblasts due to efforts at regeneration, the connective tissue increases greatly in amount. This is shown by the fact that where the treponemata are most numerous (Fig. 15) the connective tissue is most abundant (Fig. 16). Later as the collagen fibrils contract the liver cells are compressed and more or less atrophy accordingly results. This diffuse type of lesion, due to primary increase of connective tissue and secondary atrophy of liver cells, is perfectly well recognized as characteristic of congenital syphilis. It is not infrequently complicated with focal lesions (miliary and larger gummata) due to occlusion of the sinusoids, necrosis of the liver and other cells in the area affected, and inflammatory infiltration with serum and polymorphonuclear or endothelial leucocytes.

In acquired syphilis the early lesion in the liver is diffuse (Fig. 17) and similar to that in congenital syphilis but occurs in larger and smaller foci only and usually leads to necrosis and inflammatory infiltration, forming the characteristic gummata of this type of infection, which later may heal and contract, resulting in deep scars and more or less lobulation of the liver.

If this reading of the lesions occurring in syphilis is correct, then although the gross manifestations are many and varied, the cellular reaction caused by the treponema pallidum is essentially the same in all of them and varies only in degree, due to varying conditions of injury and reaction and of local and general immunity.

V. Alcoholic Cirrhosis.

In the chronic, progressive, so-called alcoholic, type of cirrhosis there occurs a peculiar form of necrosis of the liver cells, which seem to be characteristic of it. The cytoplasm of the cells first undergoes a degenerative change in consequence of which an irregular, coarse, hyaline meshwork (Fig. 18) appears in it. This meshwork stains deeply with eosin and with phosphotungstic acid hematoxylin after fixation in Zenker's fluid. This degenerative change may attack single cells or small or large groups (Fig. 19) of them: it may occur focally or very diffusely. The affected cells may be situated in any part of the lobule, but lie most commonly, perhaps, in the region of the portal vessels, and sometimes are sharply limited to that location.

The affected cells and the nuclei within them are usually swollen. After the hyaline change has reached a certain degree of intensity the cells are surrounded and invaded by numerous polymorphonuclear (Fig. 20) or endothelial (Fig. 22) leucocytes (sometimes the one, sometimes the other), which dissolve the cells, the hyaline material last, and thus bring about their disappearance.

Along with this hyaline change and destruction of the liver cells there occurs active regeneration as evidenced by occasional mitotic figures in adjoining liver cells. There is also more or less proliferative activity on the part of the fibroblasts resulting in increase of connective tissue.

These different processes of hyaline degeneration ending in necrosis, of leucocytic infiltration, of regeneration of liver cells, and of increase in the amount of connective tissue, when extensive, diffuse, and acute, lead to considerable increase in the size and weight of the liver (2400 grams in one instance). The surface of such a liver is smooth and on section the cut surface is uniformly even, the lobulation indistinct, and the consistence much increased so that the liver tissue tears with difficulty. In other cases the various changes are much less extensive and hence more chronic because they do not cause death so quickly.

Even in the latest stages of alcoholic cirrhosis, however, it is usually possible to find liver cells undergoing the peculiar hyaline change which seems to be characteristic of this process. Still it is not possible to deny that this destructive hyaline change may cease entirely and leave nothing but the sclerosis as evidence of what has taken place.

The increase in the amount of connective tissue causes trouble later when it contracts by occluding bile ducts and blood vessels here and there throughout the liver. Obstruction of the bile ducts results in focal bile stasis so that scattered areas appear dark green. In these areas the bile capillaries are often greatly distended and in places ruptured so that masses of inspissated bile have escaped into the lymph spaces between the liver trabeculæ and the walls of the sinusoids. Here the masses are taken up by endothelial leucocytes and dissolved just as in the ordinary generalized bile stasis due to obstruction of the common duct.

It is not at all uncommon to find all these different processes (hyaline degeneration, leucocytic infiltration, regeneration, proliferation of connective tissue, and focal bile stasis) present in one and the same liver section.

The obstruction to the general flow of blood through the vessels resulting in portal stasis and ascites needs no mention here.

This type of cirrhosis is very commonly complicated by fatty infiltration (Fig. 21) which leads to marked increase in the weight of the liver (3315 and 3580 grams in two instances, and greater weights are on record). As a rule the clinician's diagnosis of hypertrophic cirrhosis proves to be of this nature. So far as can be determined from histological observation, the presence of the fat interferes in no way with the degenerative process. Cells filled with one or more fat vacuoles undergo hyaline change like the others.

The cause of the increase of the connective tissue in this type of cirrhosis is not perfectly obvious. The primary injury affects the liver cells and is followed by more or less regeneration of them. We have seen perfectly clearly in the first type of cirrhosis (that following extensive central necrosis), that injury to the liver cells does not result in proliferation of fibroblasts. On the other hand we have, in alcoholic cirrhosis, around and invading each necrotic cell, an acute inflammatory exudate of leucocytes which must cause more or less stretching of the connective tissue. The injury which results in proliferation of fibroblasts seems, therefore, as in pigment cirrhosis to be mechanical in origin, not toxic.

If we leave tumors out of the question, the only other common cause, besides direct toxic or mechanical injury to fibroblasts, which stimulates them to proliferate is the presence of fibrin and that plays no part in this form of cirrhosis.

It has long been a much disputed point, chiefly with reference to the alcoholic type of cirrhosis, whether the number of bile ducts in certain cases is greatly increased or whether many of them are not compressed columns of liver cells. The type of necrosis following central necrosis shows that bile ducts may grow out to a considerable distance towards the hepatic vein. In infectious cirrhosis a similar prolongation of bile ducts may occur. On the other hand the diffuse form of syphilitic cirrhosis shows that liver cell trabeculæ may be greatly compressed so as to resemble to some extent bile ducts. Therefore, it is theoretically possible that both true and apparent bile duct formations may occur in alcoholic cirrhosis. As a matter of fact both probably do. If these so-called bile ducts are carefully studied after proper staining it will often be found that in some of the epithelial cells composing them hyaline material similar to that in the degenerating liver cells is present (Figs. 23 and 24). Likewise in alcoholic cirrhosis complicated with fatty infiltration fat vacuoles will occasionally be found in the cells (Fig. 24) which look like bile duct epithelium. The presence of the fat vacuoles and of the hyaline material proves beyond question, it seems to me, that the cells containing them are compressed liver cells and not bile duct epithelium.

The terms hypertrophic and atrophic cirrhosis cause the student and the clinician much trouble. This analysis of these five types of lesions shows that we may get a large, hypertrophied, smooth liver in at least three of them, in infectious, pigment, and alcoholic cirrhosis. It is due in each instance to an extensive, diffuse, acute process. If the acute lesion ceases and healing takes place, or if the process is of moderate intensity and long duration so that healing and scar tissue are more prominent than degeneration and exudation, the liver will diminish in size below the normal. The cirrhotic liver following central necrosis is necessarily at all stages below the normal in weight.

Atrophic cirrhosis simply means a liver in which a large proportion of the liver cells have been destroyed and have disappeared, while the existing and new-formed connective tissue have been rendered unduly prominent.

The terms monolobular and multilobular cirrhosis are also extremely confusing. They state only a relation between masses of liver cells which rarely correspond to liver lobules and strands of connective tissue. They do not in the least explain the nature of the process. In infectious cirrhosis the lesion is confined quite uniformly to the portal vessels: the same is true to a less degree of pigment cirrhosis. If, after old custom, the hepatic vein is taken as the center of the lobule, then these two types of cirrhosis may be said, perhaps, to deserve the term monolobular.

In syphilitic cirrhosis of the diffuse type the sclerosis spreads quite evenly throughout every lobule.

In cirrhosis following central necrosis, large groups of lobules are completely sclerosed, while other large groups may be perfectly normal. The lesion is most irregular in distribution.

In alcoholic cirrhosis the distribution and intensity of the degenerative process vary greatly in different cases, and the increase of the connective tissue follows in the same lines. It often cuts into lobules in every direction. At other times it is fairly regular in its distribution. As a rule, however, the lobular arrangement is quickly distorted. Hepatic veins are hard to find. Sometimes the more normal areas are small, at other times large so that on gross examination either term, mono- or multilobular, might be appropriate. It must also be borne in mind that regeneration of liver cells plays an important rôle in alcoholic cirrhosis and may lead to comparatively large areas of newly formed liver cells, showing no lobular arrangement, containing no bile ducts, and sometimes regarded as adenomata.

It would seem much wiser to discard these terms which do not explain and serve only to confuse. They emphasize the wrong end of a pathological process and represent only the result of two forces acting against each other, the expanding efforts of regenerating liver cells, the contracting force of the proliferated fibroblasts which tend to squeeze the surrounded liver cells into the narrowest compass, namely, into spherical masses.

Granting that cirrhosis may arise in the ways described from at least five different types of lesions, is it possible, in the case of a given sclerosed liver, to determine what the nature of the acute process was to which it owed its origin? I am inclined to think that in most cases, perhaps in all, it is possible to do so, if the characteristics of each type are clearly comprehended and if the sclerosed liver is carefully examined.

Conclusions.

At least five different types of lesions may terminate in cirrhosis (sclerosis) of the liver: one is acute, the other four more or less chronic in character.

Toxic cirrhosis (following extensive central necrosis) demonstrates clearly three facts:

1. That when all the liver cells of a lobule are destroyed the bile ducts grow out a certain distance towards the hepatic vein, but that they do not produce liver cells.

2. That liver cells regenerate only from liver cells, never from bile duct epithelium.

3. That fibroblasts (connective tissue cells) do not proliferate when liver cells alone are destroyed.

The other four types of lesions terminating in cirrhosis show that fibroblasts multiply (regenerate) only when fibroblasts themselves have been injured or destroyed and thus lead to increase of the connective tissue.

The so-called alcoholic type of cirrhosis is characterized by a peculiar hyaline degeneration of the cytoplasm of the liver cells preceding necrosis. In this same type of cirrhosis the contraction of the connective tissue frequently compresses groups of liver cells so that they may resemble bile ducts: in

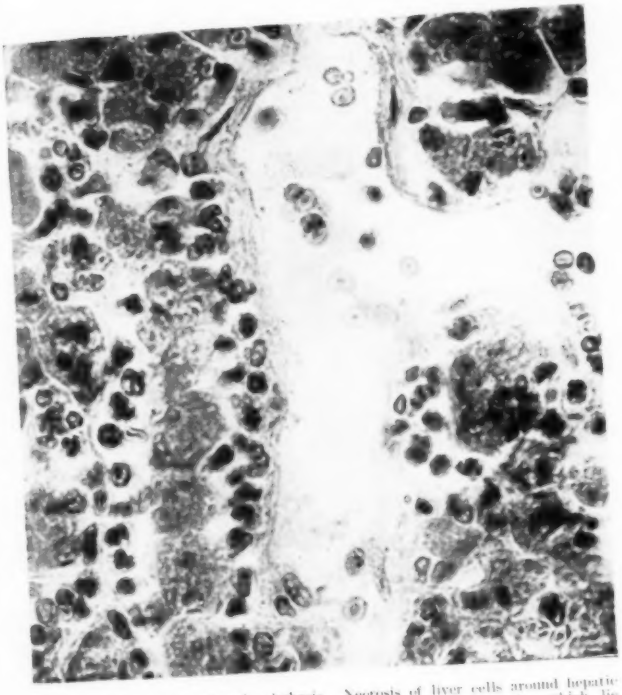

FIG. 1.—First stage of toxic cirrhosis. Necrosis of liver cells around hepatic vein (central necrosis); invasion by polymorphonuclear leucocytes which lie mostly between the necrotic liver cells and the walls of the sinusoids.

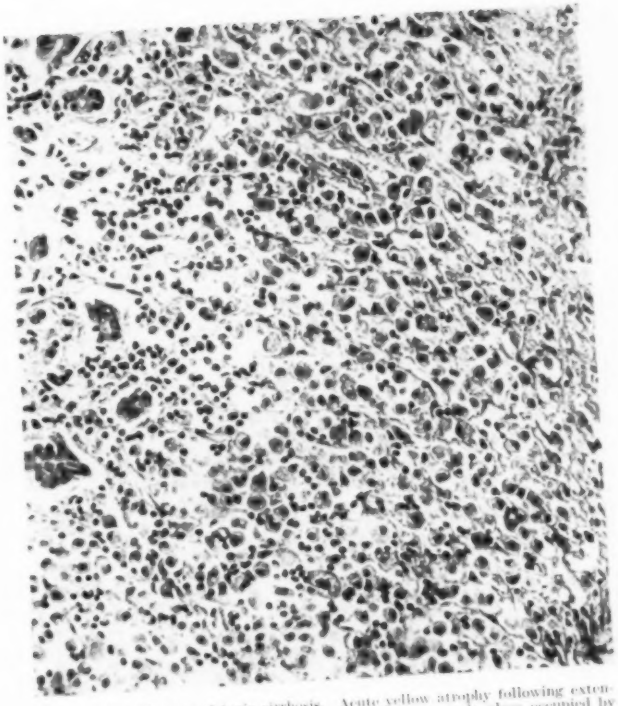

FIG. 2.—Second stage of toxic cirrhosis. Acute yellow atrophy following extensive central necrosis. Liver cells all destroyed and removed; place occupied by large numbers of endothelial leucocytes.

FIG. 3.—From same case as Fig. 2 showing a small group of liver cells from which regeneration may take place.

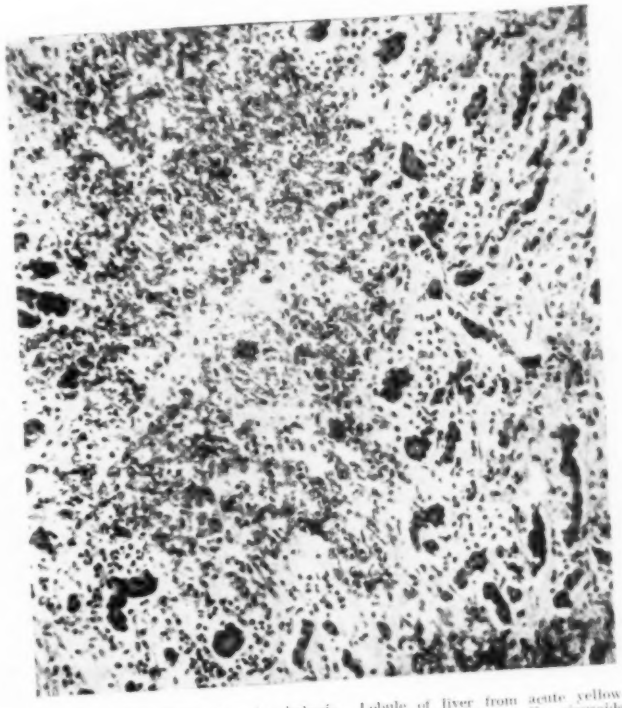

FIG. 4.—Late stage of toxic cirrhosis. Lobule of liver from acute yellow atrophy after repair has taken place. No regeneration of liver cells; sinusoids filled with blood; bile ducts have extended part way towards the hepatic vein and then stopped; contraction and thickening but no increase of connective tissue.

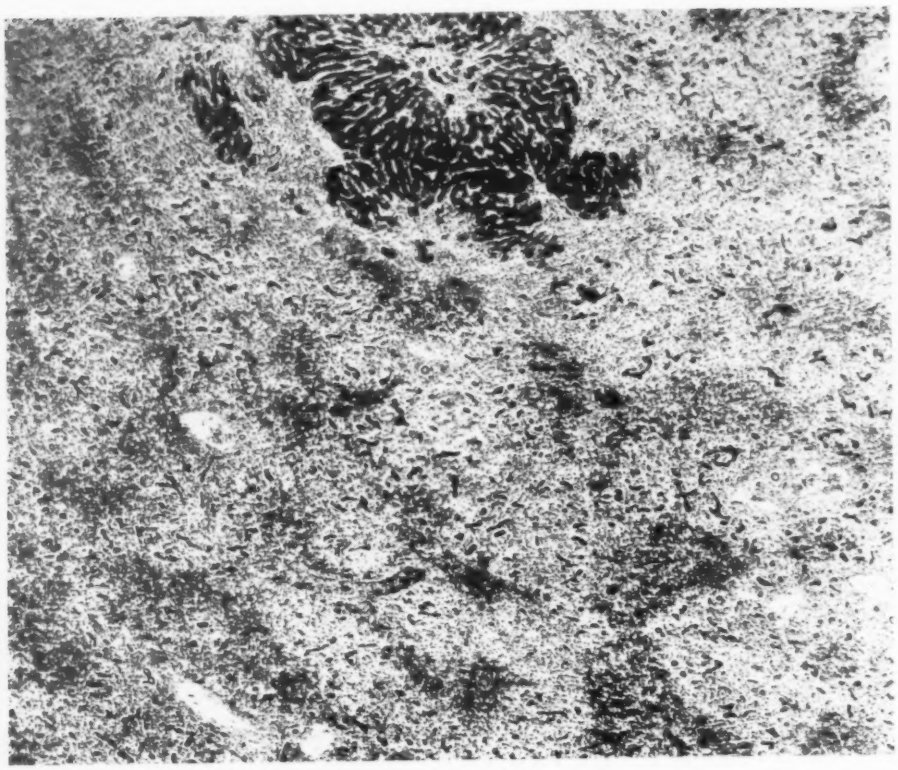

FIG. 5.—Late stage of toxic cirrhosis. Sclerosis of liver following extensive central necrosis and acute yellow atrophy. Lobular arrangement preserved but shrunken; bile ducts prominent.

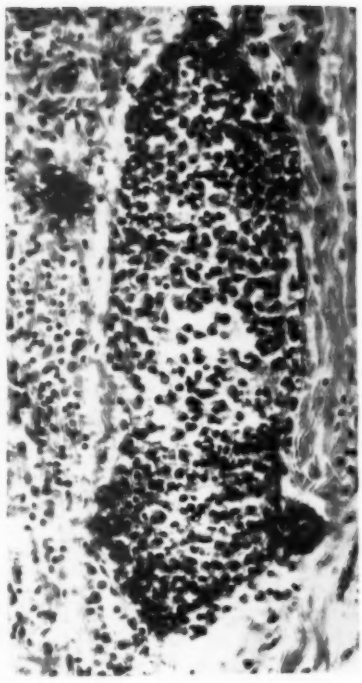

FIG. 6.—Early stage of infectious cirrhosis. Lymphatic in capsule of liver dilated and filled chiefly with endothelial leucocytes.

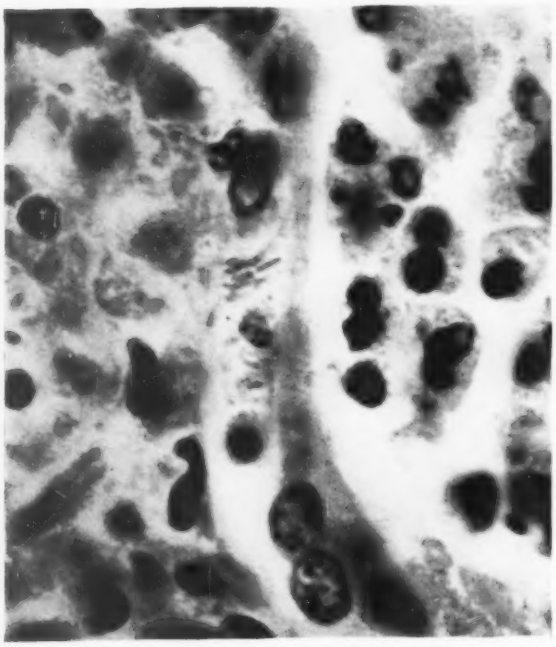

FIG. 7.—Early stage of infectious cirrhosis. Bacilli present just outside of a distended bile duct filled with leucocytes.

FIG. 8.—Early stage of infectious cirrhosis. Bile ducts dilated and filled with endothelial leucocytes.

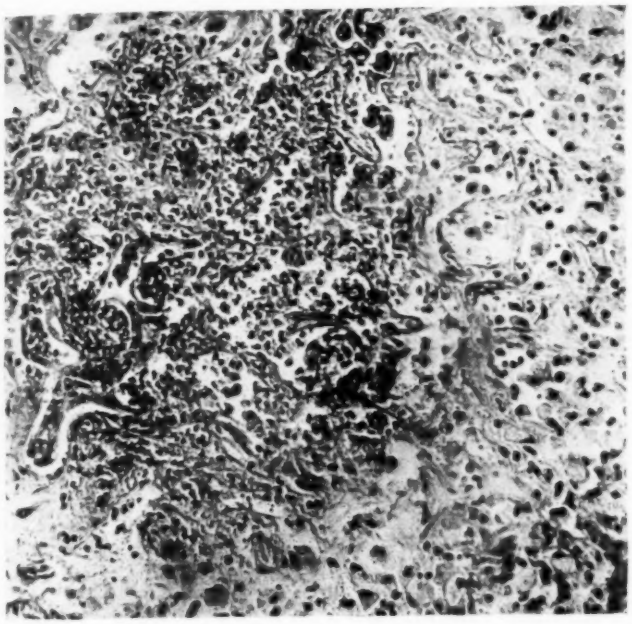

FIG. 9.—Bile stasis complicated by infection along bile ducts. Area of necrosis infiltrated by polymorphonuclear leucocytes.

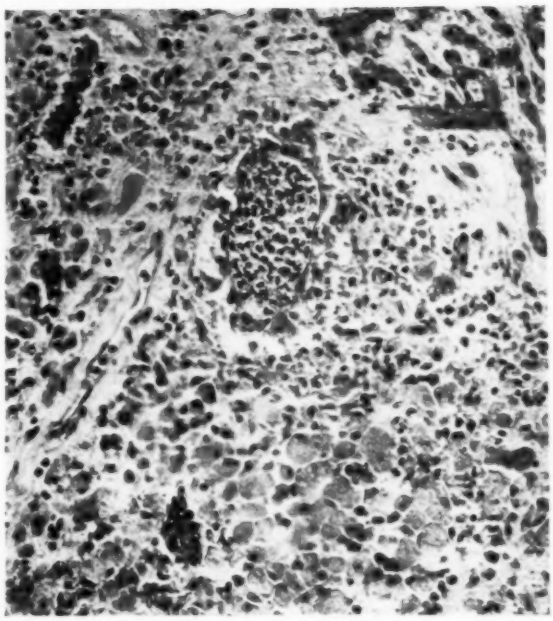

FIG. 10.—Early stage of infectious cirrhosis. Bile duct distended and filled with polymorphonuclear leucocytes; in adjoining area of softening chiefly endothelial leucocytes containing bile and fat.

FIG. 11.—Early stage of infectious cirrhosis showing lesion situated around the portal vessels.

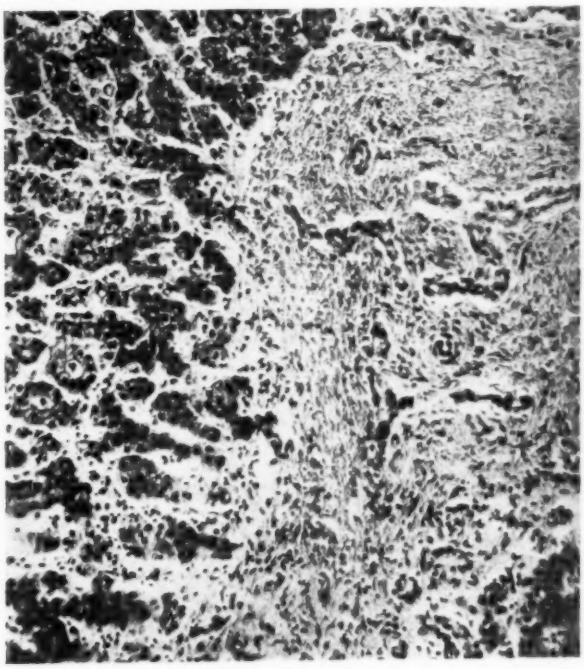

FIG. 12.—Late stage of infectious cirrhosis after repair has taken place.

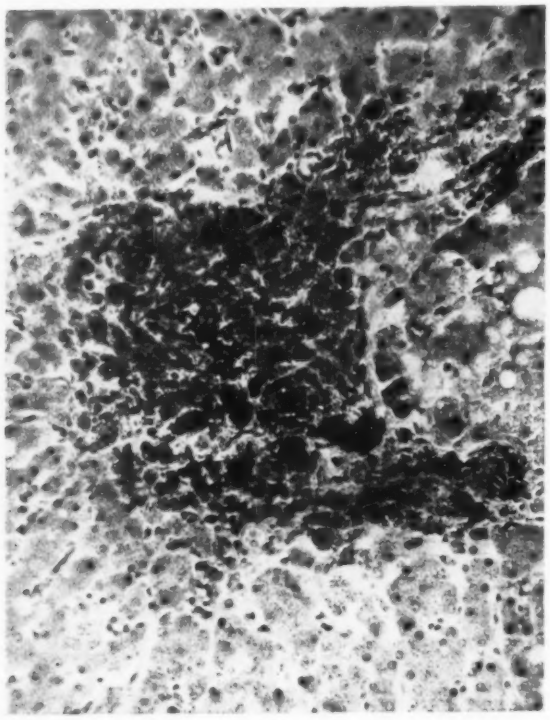

FIG. 13.—Pigment cirrhosis from a case of hæmochromatosis showing masses of endothelial leucocytes filled with blood pigment crowding the lymph spaces around the portal vessels and mechanically causing sclerosis.

FIG. 14.—Pigment cirrhosis from a severer case of hæmochromatosis showing much pigment and sclerosis.

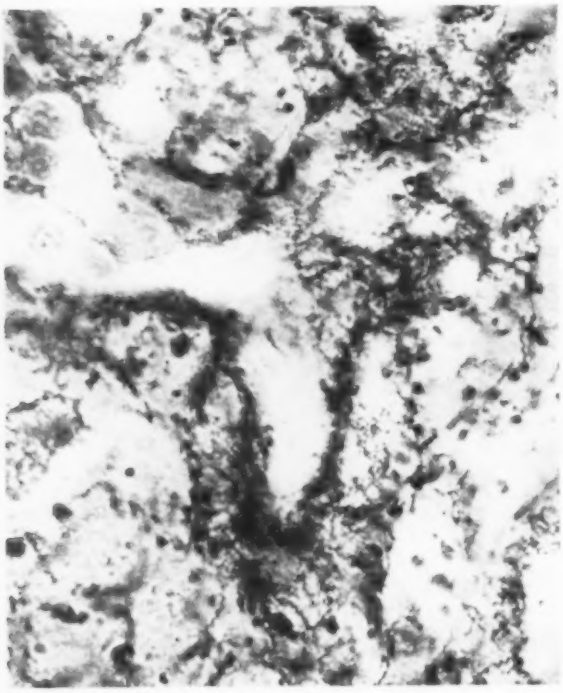

FIG. 15.—Syphilitic cirrhosis. From a case of congenital syphilis showing masses of treponemata situated in the connective tissue between the liver cells and the walls of the sinusoids.

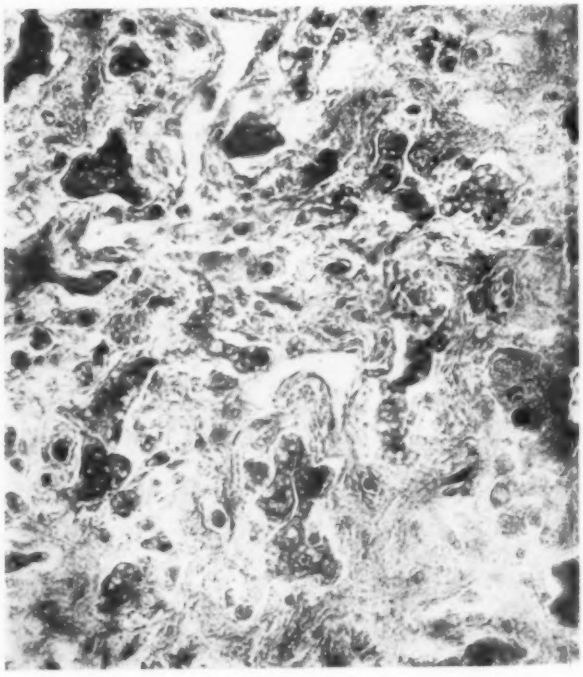

FIG. 16.—From the same liver as Fig. 15 to show the great increase of connective tissue between the liver cells and the walls of the sinusoids, which by contraction leads to compression and atrophy of the liver cells.

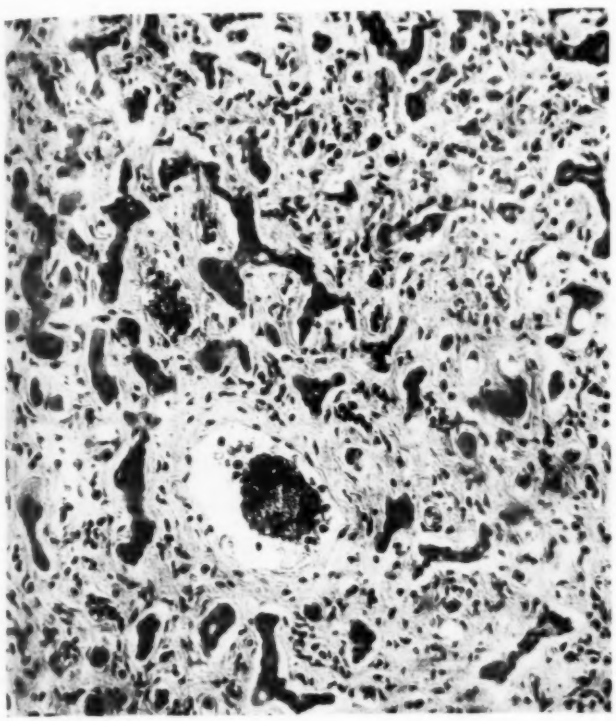

FIG. 17.—Syphilitic cirrhosis. Liver from a case of acquired syphilis in the adult showing marked diffuse increase of the connective tissue around the liver cells causing compression and atrophy of them.

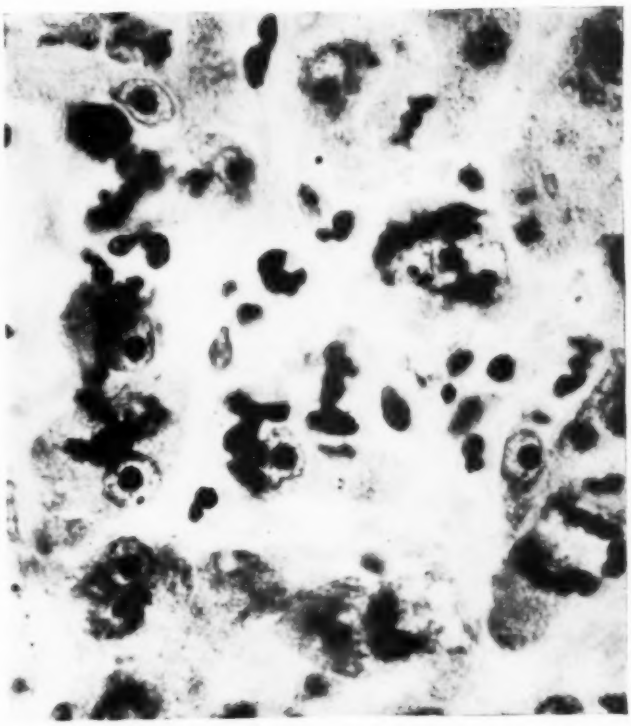

FIG. 18.—Alcoholic cirrhosis. Liver cells undergoing a peculiar hyaline degeneration before necrosis.

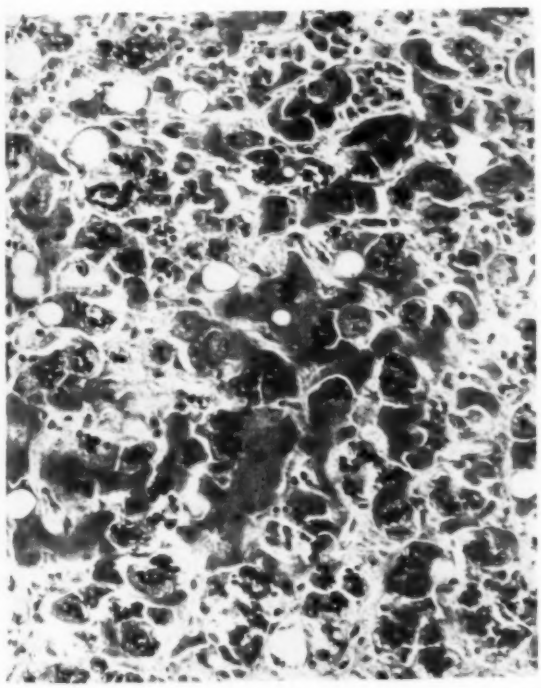

FIG. 19.—Alcoholic cirrhosis showing numerous liver cells undergoing this peculiar form of hyaline degeneration.

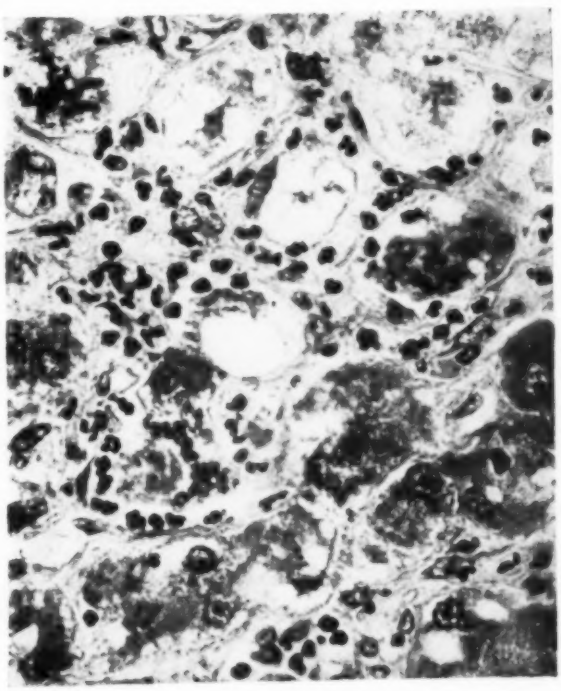

FIG. 20.—Alcoholic cirrhosis. The cells which have undergone necrosis following hyaline degeneration are being invaded by polymorphonuclear leucocytes.

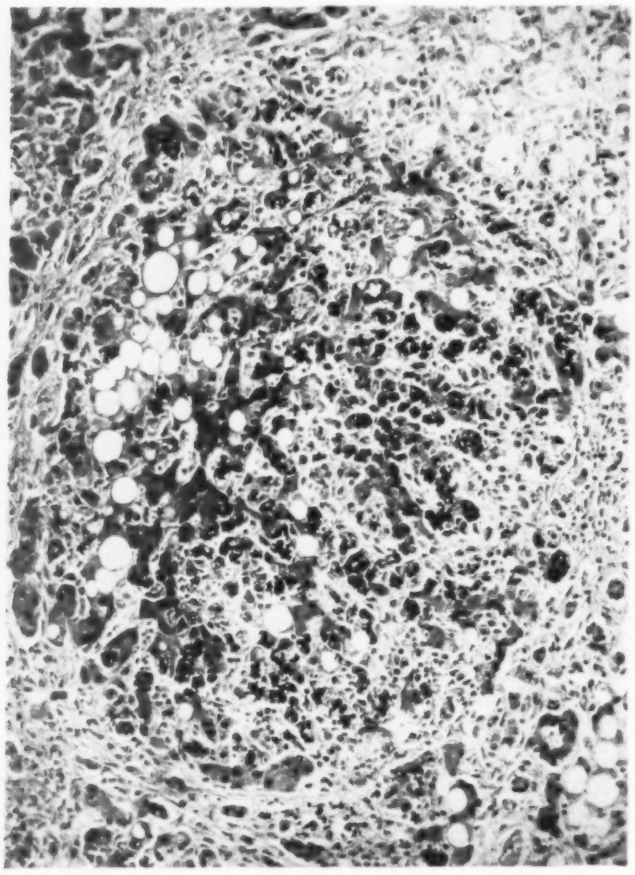

FIG. 21.—Alcoholic cirrhosis complicated with fatty infiltration.

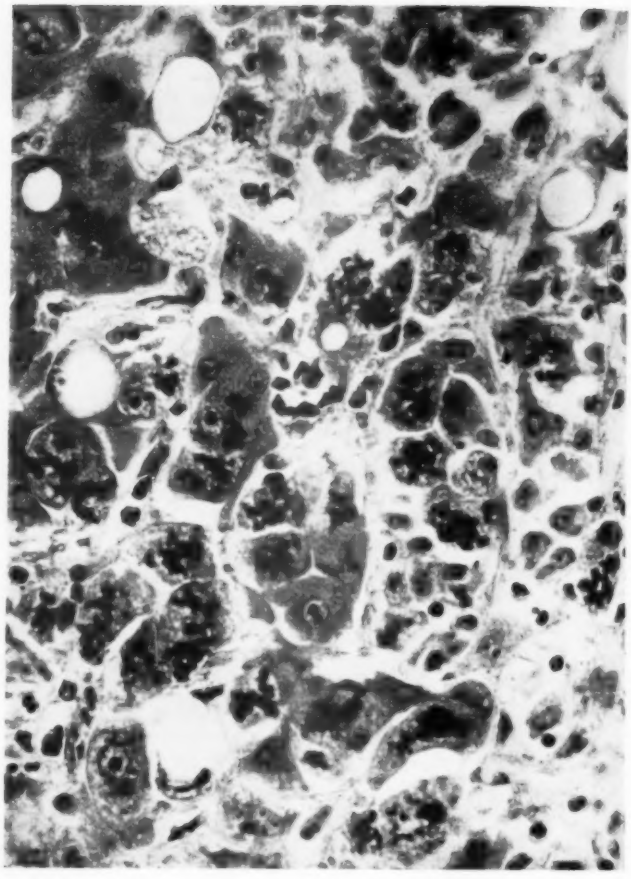

FIG. 22.—Alcoholic cirrhosis. The necrotic liver cells are being removed by the action of endothelial leucocytes.

FIG. 23.—Alcoholic cirrhosis. Compressed column of liver cells resembling a bile duct; two of the cells show the type of hyaline degeneration peculiar to the liver cells in this type of cirrhosis.

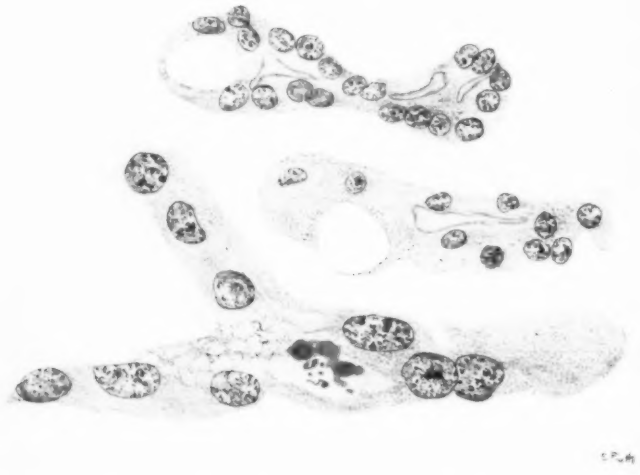

FIG. 24.—Alcoholic cirrhosis. Compressed columns of liver cells; one liver cell shows hyaline degeneration; two others contain fat vacuoles.

these compressed liver cells it is often possible to demonstrate large fat vacuoles or hyaline material due to degeneration in the cytoplasm, neither of which occurs in true bile duct epithelium.

In toxic cirrhosis the connective tissue thickens from contraction, but does not increase in amount because the fibroblasts have not been injured.

In infectious cirrhosis the fibroblasts are destroyed along with the liver cells: hence there is active regeneration and much production of connective tissue.

In syphilitic infection of the liver the primary injury is done to fibroblasts; in consequence they proliferate (regenerate), often in excess: the contraction later of the collagen fibrils produced by them results in compression and more or less atrophy of the included liver cells.

In pigment and alcoholic cirrhosis the proliferation of the fibroblasts is apparently due to injury caused mechanically by cells of exudative origin stretching the connective tissue: the reaction is similar to that produced in the lungs and peribronchial lymph nodes by endothelial leucocytes filled with carbon packing themselves in the finer lymph spaces.

For the drawings I am indebted to Miss Etta R. Piotti; for the photomicrographs numbered 7, 13, and 18 to Dr. S. B. Wolbach; for the others to Mr. L. S. Brown, of the Massachusetts General Hospital.

TYPHOID SPINE: WITH THE REPORT OF TWO ADDITIONAL CASES WITH BONY CHANGES IN THE VERTEBRÆ.

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Associate Professor of Medicine and Clinical Therapeutics, the Johns Hopkins University.

The essential character of the condition termed "typhoid spine" has been the subject of much controversy but the findings of recent years have settled the question in favor of definite organic changes—a spondylitis—as against a neurosis. In 1906 the writer[1] reported two cases of typhoid spine in which the occurrence of bony changes in the vertebræ was proved by the skiagrams. At that time, while the occurrence of bony changes in the form of kyphosis, etc., had been noted, there had not been any report of bony changes as shown by skiagrams. Since then several such cases have been reported and in the present paper two additional ones are described.

Case 1. *Typhoid fever in Nov.*, 1908; *tetany (?); recovery; discharged Jan.* 8, 1909. *Symptoms of typhoid spine, March* 15, 1909. *Second admission Apr.* 17, 1909. *Second attack (relapse?) of typhoid fever Apr.* 26, 1909; *recovery.*

The patient was a white male, aged 45 years, by occupation a laborer. His family history was negative and in his personal history the only illness was an attack of malaria in July, 1908. He had formerly been a very heavy drinker but had taken no alcohol for six months before admission. *First admission, Nov.* 9, 1908. The present illness began with headache, weakness, anorexia and general malaise. Apparently at times he had been slightly delirious as there was a history of his wandering about the house in an aimless way. He was admitted on the sixth day of the disease. On admission the tongue was coated; some râles were heard over both lungs; the heart was clear. There were fairly numerous rose spots on the chest and abdomen and the spleen was palpable. A blood culture gave typhoid bacilli, and the Widal reaction was positive on the day of admission and again on the 16th day. The patient showed signs of marked toxæmia, but the only feature of special interest was the occurrence of a condition much like tetany during the course of the disease. There was marked flexion of the toes and the hand was held in the position seen in tetany, this becoming much more marked when the cuff of the blood pressure apparatus was applied to the upper arm. The temperature became normal on the 37th day of the attack and the patient was discharged in good condition on Jan. 8, 1909. During his convalescence there was no complaint of any pain or discomfort in the back and he felt well on leaving the hospital.

[1] Am. J. Med. Sc., 1906, CXXXII, 878.

Second Admission—April 17, 1909.—After discharge from the hospital he did not return to work until Jan. 30, when he resumed his occupation in the blacksmith department of the works where he was employed. This involved some heavy lifting but he was quite sure that there had not been any injury or strain. He felt perfectly well until March 15, when he began to have pain in the lower part of the back; there was no other symptom. The onset was gradual and he was able to continue at work for one week but then had to give up on account of the severity of the pain. This was not constant but came on in paroxysms which lasted from 15 to 20 minutes. The patient commented on the effect on his general condition, remarking that the pain had made him "weak and discouraged." He emphasized the fact that the pain was much worse in the night than during the day and attributed his feeling so badly to loss of sleep rather than to the pain.

Examination.—The patient's general condition was good. The lungs were clear throughout except for a few râles at the bases. The heart was slightly increased in size, the impulse being feeble; the sounds were rather distant and the first had a slight murmurish quality at the apex. The pulse was of fair volume and the blood pressure 110 mm. Hg. The abdomen was negative; no rose spots were seen and the spleen was not felt. The abdominal walls were soft; there was no contraction of the muscles. The hæmoglobin was 86 per cent, red cells 5,100,000 and leucocytes 5700 per cmm. When the patient stood up there was a rather well marked scoliosis in the lumbar region and the right shoulder was held higher than the left. The usual lumbar lordosis was almost obliterated. There was very little movement of the lower spine when the patient bent forward and to the left or right and there was practically no movement in the lower spine when he bent backward. The spine showed very little movement below the tenth thoracic vertebra. On palpation there was some tenderness on both sides of the lumbar spine but no tenderness on pressure over the spinous processes of the vertebræ. The muscles on both sides were contracted and stood out prominently, this being more marked on the right side. The knee jerks and tendo Achillis reflexes were rather more active than normal and equal on the two sides, but the arm reflexes showed much the same increase. There was a normal response to plantar stimulation. At this time the patient had slight fever, about 100° F., which disappeared in the next three or four days. For the next five days the condition was practically the same. There was slight tenderness on pressure over the lower spines, especially about the fourth

lumbar vertebra, and distinct tenderness on either side especially to the left of the fourth and fifth lumbar vertebræ. As long as the patient made no movement he was fairly comfortable but when asked to stand on his toes and come down forcibly on the heels he did this very slowly and carefully. When he walked the back was held very stiffly and when he tried to get out of bed he had great difficulty in doing it, the back being held rigidly and the patient bracing himself as much as possible by the arms. The abdominal muscles at times were held very rigidly. When the patient was flat in bed the lumbar lordosis seemed to be obliterated and there was marked rigidity of the muscles on both sides of the spine in this region. The *X-ray plate* on April 22d showed marked ossification of both lateral ligaments in the lumbar region and also a suggestion of this in the anterior ligament (Dr. Baetjer).

About this time for a period of two days, the patient was unable to void urine and he had to be catheterized. On April 23d the temperature rose to 100° F., and the next day to 103° F., which proved to be the beginning of a typical attack of typhoid fever. A blood culture on April 26 (the fourth day of the fever), yielded typhoid bacilli and the Widal reaction was also positive. On April 27, it was noted that the spleen was enlarged and palpable. No rose spots were made out. During the illness the patient suffered greatly from the pain in the back, at times this being extremely severe. His expression of apprehension when anyone came near the bed, fearing that they might touch it and so cause him pain, was always striking. He looked very haggard and ill, and remained absolutely motionless unless he had to move; this was done with great deliberation and care and there was no doubt of the severity of the pain. Examination showed no disturbance of sensation in the legs; ordinary sensation, pain and temperature sense all seemed normal. The attack of fever was not very severe; the patient did well and the temperature reached normal on May 8, the 16th day of the attack or relapse. The blood count showed a slight drop, as the hæmoglobin was 80 per cent, red cells 4,460,000 and the leucocytes 6800 per cmm. The leucocyte counts throughout were between 6000 and 7000. The urine showed a specific gravity usually between 1014 and 1028; there was no albumin or sugar. A positive diazo reaction was given once. The blood pressure was low, generally between 80 and 100 mm. Hg., averaging about 90 mm. Hg.

On May 20, a plaster cast was put on with the patient in a hammock. A second one was applied a week later and the patient was much more comfortable. At this time he complained very little of pain and got about without much difficulty. There was no evidence of any wasting in the legs more than is usual after an attack of typhoid fever. The leg reflexes were rather active but equal on the two sides and sensation seemed perfectly normal. The X-ray plate showed the same changes in the vertebræ as before. He was discharged in good condition on June 8.

On July 18, 1909, the patient was seen and found to have been improving slowly. He had not returned to his usual employment but had been doing a certain amount of light work which did not involve much exertion. He had been wearing a plaster jacket and stated that he suffered very little from pain in the back although he had felt weak. Two days before this examination he removed the plaster jacket and since then has had rather more pain. Examination of the back did not show any change in the spine but the muscles on the right side were still definitely more contracted than on the left. There was no kyphosis and no definite scoliosis. What pain the patient had was referred to the lumbar region but there was no tenderness on pressure over the spine. The reflexes in the legs were still much exaggerated. Four months later he was practically well.

Remarks.—One point of interest is the occurrence of a relapse or second attack between five and six months after the original attack. Whether this should be termed a relapse or a second attack is difficult to decide, for there is no period which can be set as a dividing line between a relapse and a second attack. The case here reported is much like one previously described by the writer,[2] in which the original attack began on June 2, the patient being convalescent in March when the symptoms of typhoid spine appeared. He was admitted to the hospital on July 4 of the same year for the spinal symptoms, and a week later the second attack (or relapse) of typhoid fever began. In both these cases there was an interval of months between the attacks, in which the symptoms of spondylitis appeared. One explanation of the cause of typhoid spondylitis is that there are local lesions in the bone in which typhoid bacilli are present. It is tempting to suggest that this focus may have been the source of the second infection in these cases. However, our knowledge of what determines relapses is not very satisfactory and it would be easier to regard the second febrile attack in these two cases as a second attack rather than as a relapse. Besides the retention of typhoid bacilli in the body after recovery from an attack of typhoid fever is so common (e. g. in the gall bladder) that we should not attach too much importance to such a source of reinfection.

Case 2. *Typhoid Fever in June, 1909; intestinal hemorrhage; phlebitis; recovery; discharged Aug. 14, 1909. In October, 1909, neuritis of the right external popliteal nerve; spondylitis found.*

The patient was a white male, aged 45, whose occupation was a worker in a factory in which he did a great deal of heavy lifting. The *first admission* (Medical No. 24248) was on June 14, 1909, when he came complaining of cough. There was no history of arthritis and he had not used alcohol. He had always been a hard worker and a heavy eater. His illness began eight days before admission when he received a severe wetting. For a day or two after this he felt dizzy and had some indefinite trouble in the head; this was much worse after he spent some hours working in a hot room. There was also some headache and indefinite pains about the chest. On examination the patient was a healthy looking man with a good color. The percussion note over the lungs was rather hyperresonant and there were a few râles heard on both sides of the chest; the heart was clear. The abdomen was natural; no rose spots were found and the spleen was not felt. Four days after admission the temperature fell to normal and then rose again, at one time reaching 105° F. Definite rose spots appeared and there was slight jaundice. On June 22, about the 16th day of the illness, the patient passed blood from the bowel, but the hemorrhage was not severe, and made no change in the patient's general condition. On June 21, the 15th day of the disease, the blood culture was positive, typhoid bacilli being obtained. The course was without any special features till he began to get up out of bed on August 8, when he complained of some pain in the right leg, both in the popliteal space and below the knee. The leg was somewhat swollen below the knee; the skin had a shiny appearance and was quite sensitive to the touch. There was definite swelling and the circumference of the right calf was 3 cm. greater than the left. This was regarded as a mild attack of phlebitis and subsided before discharge on August 14th.

For a time after leaving the hospital both legs were very weak, especially below the knees and the swelling and pain in the right leg returned after discharge. In from two to three weeks the weakness of the left leg had disappeared entirely but the right

[2] *Loc. cit.*

leg did not improve as rapidly and it was only after a period of about six weeks that the pain and swelling in the right leg disappeared and the patient was able to walk about without any special discomfort. During October the patient was seen several times in the out-patient department. His complaint was especially of dizziness and weakness, but he stated that he had not suffered from any pain. He had chronic ear trouble for which he had been treated some time before and the aurist considered that this was possibly responsible for the dizziness. The patient had made several attempts to resume work but found that he had not sufficient strength and that when he went to do any heavy lifting he was apt to stagger. It was not possible to obtain the history of any special strain or injury during this time and no definite evidence of spondylitis could be found although the patient was repeatedly examined with this in mind. There had not been any pain in the back and it was difficult to test the movements of the spine as on any attempt at bending the patient complained of dizziness and was afraid of falling. In the absence of any definite symptoms suggesting spondylitis it was not thought necessary at this time to have an X-ray plate taken. During this time he had gained twenty pounds in weight and was a good deal stronger.

Towards the end of October the patient began to complain of trouble in the right foot. He stated that at first there was numbness over the upper part of the foot and especially in the great toe; later he had some difficulty in walking as he was unable to properly lift the foot. On October 27, it was found that he had some difficulty in walking and that the right foot dragged a little. A few days later he complained of a good deal of pain in the right foot, and the gait was distinctly more affected. The knee jerks were present on both sides but the ankle jerk was decreased on the right. He had no power of movement in the right great toe and had difficulty in lifting the foot. In view of the condition he was admitted to the hospital November 9. (*Second admission*). On examination the patient's general condition was excellent; the lungs and heart were clear throughout. The abdomen was normal and the spleen was not felt. On examination of the legs it was found that there was marked foot drop on the right side with marked weakness of the extensors of the right foot. Voluntary dorsal flexion of the right foot was possible but the right great toe could not be flexed or extended except that slight flexion occurred when the other toes were moved. Passive movement of the great toe was possible in any direction. The knee jerk on the right side was much more marked than on the left. Plantar response was normal on the left side but could not be obtained on the right side. There was no ankle or patellar clonus. The superficial veins of the right leg were definitely dilated but there was no œdema of the feet or ankles, and well-marked pulsation was present in the dorsalis pedis artery on both sides.

Over the dorsum of the right foot, from the ankle along the mesial margin, including the right great toe and extending to the tendon of the extensor digitorum longus, sensation to touch was much affected and the response to pain and temperature stimuli was rather inaccurate. Along the medial border there was an area of hyperæsthesia; pain stimuli caused a marked contraction of the rectus femoris, almost approaching a spasm. There was no atrophy of the calf muscles and there did not seem to be any difference in the strength of the hamstring muscles of the two legs. The sensory disturbances cleared rapidly and disappeared by November 25. On electrical examination it was found that with the galvanic current the affected nerve did not respond to stimuli; the muscle itself responded to a strong current, the ccc. being stronger than the acc. With the faradic current the nerve did not respond; the muscle responded sluggishly and less so than the muscle on the other side.

The *X-ray plate* by Dr. Baetjer showed a definite deposit of bone on the left side of the spine between the articulations of the III, IV, and V lumbar vertebræ, which practically obscured the articulations. The bone was deposited on the lateral ligaments and the anterior and posterior ligaments seemed free. There was no deposit on the right side.

During this time the patient's temperature was practically normal, and he was discharged much improved after being ten days in the hospital. The patient's condition improved steadily after this and in January, 1910, the signs in the right leg had practically disappeared. He complained that the right leg tired more quickly than the left; this may have been due as much to the effects of the phlebitis as to the paralysis. By the beginning of March the patient seemed perfectly well. He did not make any complaint of pain in the back and the movements of the spine seemed normal except for slight limitation in the lumbar region. He had returned to work and seemed able to do this without difficulty.

Remarks.—This case is unusual in several particulars. In the first place it shows that typhoid spondylitis may occur without any severe pain. The symptom of pain has been regarded as the most essential one in "typhoid spine" and it is very evident in this case that but for the radiogram the diagnosis of spondylitis could not have been made. In this event the condition in the popliteal nerve would have been regarded as a post-typhoid neuritis and the causal influence of the local process in the spine would not have been recognized. The involvement of the nerve root on the opposite side to that on which the deposit of bone occurred is seen not infrequently in cases of spondylitis.

The Nature of "Typhoid Spine."—Formerly the term was applied to a symptom picture regarded by many as being a neurosis in the majority of cases. That it may be a neurosis in some cases is quite possible but the increase in our knowledge of the organic changes which occur in "typhoid spine" speaks against this view. This is upheld by the fact that as the condition was studied more carefully an increasing number of cases have been reported with evidence of definite bony changes, supporting more and more strongly the view that it is a spondylitis. This is analogous to the change in our views regarding spondylitis generally. The work of recent years has shown that many of the cases formerly regarded as lumbago, "rheumatism," etc., are instances of spondylitis, probably associated with various organisms in different cases. The proportion of cases of "typhoid spine" with bony deformity or shown by the X-rays to have bony changes is comparatively large, in fact as large as could be expected. Spondylitis is of very varying degree in different cases and many of those which we see with other conditions—such as arthritis deformans when a spondylitis is part of a multiple arthritis—give no positive evidence of bony changes either by deformity or by the X-rays.

In 1907 Silver[3] collected 67 cases of typhoid spine of which 14 were rejected for various reasons, leaving 53 fairly definite cases. Among 51 of these in which the sex was stated only six

[3] "Typhoid Spine; a report of a case with radiographic evidence of structural change; analysis of the reported cases; complete bibliography." The Am. J. Orthop. Surg., 1908, V, p. 194. In the same volume is an article by Myers, "Typhoid Spine with special reference to the deformity." These are two interesting and comprehensive articles which should be read by all interested in the subject.

were females. In making this collection Silver excluded those cases in which a neurosis seemed probable. Myers found in his study that kyphosis had been noticed in 36 per cent of the cases. It seems a fair inference that in a large number of cases with an actual spondylitis this need not proceed to the extent of causing external bony change. However, the number of cases with external bony deformity, considered with the number in which radiographs show bony changes, points to the probability that the symptoms are due to a definite process in the spine or its attachments. To decide this question as far as possible the various changes which suggest definite local changes may be considered.

1. *Local swelling.*—This has been frequently noted and Silver found it reported in 14 (26 per cent) of his collected series. Redness has been present in a few cases, tenderness in many more, sometimes over the spine, sometimes over the adjacent muscles. Rigidity of the spine has been quite common and may be considered to be almost invariably present.

2. *Changes in the spine.*—Kyphosis was noted in 15 of his series by Silver and by Myers in 20 of 56 cases (36 per cent). The descriptions of this vary considerably but it is fair to say that some degree was present in one-third of the cases. Scoliosis was noted in some cases, in nearly all of which it disappeared after an interval. Alteration of the lumbar curve is not uncommon.

3. *Evidences of involvement of the nerve-roots.*—These while variable, still are suggestive of organic changes. Sensory disturbances are common and alterations in the reflexes occur in a large proportion. In some cases the symptoms evidently were due to changes inside the spinal canal causing pressure on the cord. In one of the cases previously reported by the writer there was marked atrophy of the muscles of one leg. The second case here reported is of special interest in this connection.

4. *Radiograms.*—These have shown definite evidence of bony changes in a sufficiently large number of cases to support strongly the view that organic changes are the rule in typhoid spine. It must be remembered that many cases of spondylitis do not show any definite bony changes. Brief mention of some of the findings may be made. In the two previously reported by the writer there were definite deposits of new bone in the lower spine. In Silver's case there was a slight curving of the spine to the left at the juncture of the first and second lumbar vertebræ in the first plate, which had disappeared when a second plate was taken. On the left side of the spine no line of separation between the bodies of the first and second vertebræ could be made out, the bone was denser than normal and there was a shadow between the transverse processes which represented a deposit of new bone. In Myers' case the skiagram showed "a synostosis between the second and third lumbar vertebræ with loss of height from disappearance of the intervertebral space." Halpenny[4] in 1909 analysed 72 cases from the literature among which there were ten cases with radiographic examination, in two of which no changes were found. Some additional cases have been reported in which definite changes were found. Carling and King[5] report a case in which the "spines of the eleventh and twelfth dorsal and first lumbar vertebræ were prominent." There was also a deviation of the column to the right. The X-ray plate "showed a very dense shadow over the bodies of the ninth, tenth and eleventh dorsal vertebræ, extending laterally beyond their limits and expanding from above downwards to a point an inch outside the articular processes on the right side and rather less on the left. The right edge was rectilinear and well defined; the left edge was irregular and not so well defined below." Three weeks later "the main mass of the shadow was less dense, whilst indications of a localisation to the costo-vertebral articulations could be made out." Wilson[6] reported a case in which there was thinning of the intervertebral discs with signs of necrosis in the vertebræ and many osteophytes around them. In connection with these reports it is interesting to note that relatively very few cases of typhoid spine have been reported from Great Britain. Another case is reported by Godder,[7] in which the "X-ray of the spine shows a diseased condition of the vertebræ at the level of the last dorsal and first lumbar." There is no other note as to the bony changes. In Swett's[8] case there was slight lumbar kyphosis and scoliosis. The X-ray plate "showed a disappearance of the disc between the fourth and fifth lumbar vertebræ, with evidence of new bone formation and the scoliosis beginning at this point." In a recent article Frick[9] reports three cases without mentioning an X-ray examination. He discusses the whole question at length and gives an excellent bibliography. One of his cases showed the curious rhythmical contractions of the abdominal muscles which were noted in one of our earlier cases. In Frick's patient the contractions were synchronous with the pulse. Potter[10] has reported a case in which the X-ray plate showed "a very definite lesion in the intervertebral disc between the tenth and eleventh dorsal vertebræ. The spacing between these vertebræ is reduced to about one-half the size it is between the others." There was an increase in the density of the lower part of the tenth and upper part of the eleventh dorsal vertebræ.

5. *Suppuration.*—The occurrence of suppuration is worthy of mention. It has been pointed out that if the condition is due to the local action of typhoid bacilli, suppuration might be commonly expected, as typhoid bone lesions in general show a marked tendency to pus formation. Yet one of the prominent features of typhoid spine is the absence of suppuration. In the report of the previous cases the writer suggested that it was exceedingly probable that instances of suppuration would be reported sometime and in this connection a case reported by Myers is of interest. A diagnosis of typhoid spine had been

[4] Typhoid Spine; with the report of a case. Surg., Gynec. and Obst., 1909, IX, 649.

[5] Lancet, 1910, I, 1136.

[6] Lancet, 1909, II, 1279.

[7] Bost. M. and S. J., 1910, CLXII, 711.

[8] Yale Med. J., 1909, XVI, 119.

[9] Interstate Med. J., 1910, XVII, 815.

[10] Med. Rec., 1910, LXXVIII, 1092.

made and a plaster jacket applied. After it had been on for four weeks some odor was noticed and on removing the cast a large granulating wound was found over and to the right of the eleventh and twelfth dorsal spines. The skiagram showed a synostosis of the eleventh and twelfth dorsal vertebræ. Some question arose as to whether the abscess had originated in the bones or was due to pressure of the jacket and cultures did not decide the matter. While this case is suggestive it can hardly be accepted as definitely proved to be an instance of suppuration associated with typhoid spondylitis. An instance reported by Guyot [1] is also not positive although very suggestive. This was in a child who after an attack of what was regarded as typhoid spine, had pain in the lumbo-sacral region. On incision on both sides of the spinous processes, a large amount of pus was found but no proof obtained of any bone lesion. Two days later a focus of osteomyelitis in the left fibula was opened and a few days later one in the right thumb. The patient recovered without any deviation of the spine. However, this cannot be regarded as a definite proved case.

Certain cases in which abscess formation occurred over the lower spine may suggest a possible source in the bone but it is necessary to remember that deep bedsores may extend down to the bone and suggest an origin from it. In fact the necrosis sometimes involves the deeper tissues earlier than the skin. In the absence of positive proof it is not wise to consider these as examples of suppuration due primarily to processes originating in the bones.

Treatment.—As regards prevention it is important to remember the influence of trauma and we should warn the patients convalescent from typhoid fever to exercise care in engaging in any occupation which might throw strain on the spine. When the condition is established it is well to carry out active treatment at once as by doing this we can probably limit the extension of the process in some cases and certainly save the patient suffering. One form of treatment seems well worth a trial, the use of vaccines as in the prevention of typhoid fever. It is to be hoped that this will be tried in the future. The dosage should be the same as that employed in the anti-typhoid vaccination. In treating the established condition two points have especially to be kept in mind, the relief of pain and the protection of the spine, which, as Myers points out, is often structurally weak. The pain is usually lessened by immobilization of the spine as any movement causes great suffering. To secure this some form of fixation is required. Myers favors the use of a brace, pointing out that in the application of a support it is important not to fatigue the patient or injure the spine. He also draws attention to the importance of avoiding anything which will compress the chest. If a jacket is applied this should be done with the patient in a recumbent position and not by the suspension method. Silver mentions the use of the plaster bed and also a gas-pipe frame. It seems important to carry out whatever is adopted as early as possible after the onset of the condition. By this we may shorten the duration of symptoms and perhaps limit the amount of spinal involvement. In the first case reported here the plaster jacket was exceedingly satisfactory and gave the patient great relief. In the first of the cases previously reported by the writer, the jacket failed to give any relief and increased the pain. In such cases or before some appliance can be applied the use of counter-irritation, especially the Paquelin cautery, may give relief. Large doses of sedatives often seem to be without effect on the pain and the quantity of morphia which can be given without any appreciable relief to the patient is remarkable. The fever, which is often present, sometimes diminishes as soon as fixation is carried out, if it be due to the spondylitis. In cases in which it is due to a relapse or a second attack of typhoid fever, one must be guided by the indications. It may be very difficult to carry out any systematic method of hydrotherapy and in such cases expectant treatment is the only resort.

Conclusions.—It may be regarded as established that "typhoid spine" is a spondylitis or perispondylitis with definite local changes which may lead to the formation of new bone and so result in more or less fixation of the spine. Judging from spondylitis generally, this permanent change is less likely to occur if the proper treatment is instituted early. Many cases of spondylitis clear without permanent changes.

[1] Gaz. hebd. d. sc. méd. de Bordeaux. 1906, XXVII, 9.

ERYTHEMA MULTIFORME IRIS DURING THE COURSE OF TYPHOID FEVER.

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Before the time of Willan, the various forms of erythema, the acute exanthemata, and inflammations of the skin were grouped together, as was exemplified by the writings of Plenck (1) in 1783. In 1808 Robert Willan (2) separated the erythema multiforme group from the acute exanthemata on the one hand, and from the inflammations due to external irritants on the other. It is interesting to note that in the same volume under the heading of purpura he described what was probably a case of erythema multiforme associated with vomiting, abdominal pain, arthritic pains, and an anasarcous swelling.

In 1835 Rayer (3) cited several cases of Bonnet's to show

that the various forms of erythema might coexist, and in 1854 Hebra (4) showed that the several types of erythema multiforme were forms of one and the same malady. In 1876 Lewin (5) stated that some cases had a fatal termination, and ran the course of an acute infection, though he considered the cutaneous symptoms to be reflex in origin and frequently due to urethral irritation.

In 1895 Osler (6) first published a series of cases in which urticaria, angioneurotic œdema, erythema multiforme and purpura occurred successively or together in the same individual, and in association with a large array of visceral manifestations. Osler supplemented this article by two others, and many other writers, notably Mackenzie (7), Chenoweth (8), Neisser (9), Bulkley (10), Galloway (11) and Sachs (12) have extended this work until we know that the skin lesions of the erythema multiforme symptom complex include urticaria, angioneurotic œdema, purpura, erythema multiforme and nodosum, and if we are to believe Galloway and MacLeod (13) certain cases of lupus erythematosus as well. In the minds of the writers it is questionable whether certain other diseases, notably erythema scarlatinoides and dermatitis herpetiformis should not be included.

Visceral Symptoms.—Any one of the following visceral symptoms may occur; sometimes there are no manifest skin lesions.

Acute tonsillitis, otitis media, laryngitis, phlyctenular conjunctivitis.

Ulceration of the lips and tongue.

Temporary delirium, aphasia, hemiplegia, meningitis.

Gastro-intestinal crises with colic, vomiting, and diarrhœa.

Appendicitis, degeneration of the liver, jaundice.

Enlargement of the liver and spleen.

Bronchitis, pneumonia, pleurisy with effusion.

Endocarditis and pericarditis, anemia.

Hemorrhages from the nose, intestines, stomach, lungs, and kidneys.

Arthritis and infiltration of the synovial sheaths and periarticular structures.

Nephritis and ulceration of the cervix uteri.

Fever, usually irregular and of short duration, but often high.

Etiology.—As regards etiology there have been many theories. In 1835 Gibert (14) wrote that some cases of erythema were symptomatic due to derangements of the internal viscera. In 1850 Bulkley (15) stated that it was especially associated with digestive disturbances and gout. In 1864 Köbner (16) said that it was an angioneurosis due to vasomotor disturbances. In 1876 Lewin mentioned reflex causes, frequently urethral. Chaisse (17), Legendre (18), and Galloway (19) thought that it was due to autointoxication. Finger (20) thought that the local effect of bacteria upon the tissues caused some cases. Many writers, as Singer (21) and Howard (22) found bacteria in the blood, but in the majority of cases the technique of the blood-culture was not above criticism, and Koch's postulates were never fulfilled. As Corlett's (23) case well illustrates some at least were undoubtedly due to streptococcus infections.

Erythema multiforme is also known to occur with such definite infections as typhoid fever, diphtheria, syphilis, gonorrhœa, tuberculosis, cholera, pneumonia, leprosy, malaria, trypanosomiasis, and with suppurative processes in any portion of the body, and may also occur with nephritis and diabetes. Various drugs and antitoxins, and some articles of food also give erythematous, papular, and bullous eruptions that have the same clinical picture as the erythema multiforme group.

Erythema multiforme is frequently spoken of as occurring in typhoid, but we have been able to find only two instances where the eruption occurred during the course of the fever, the cases of Lauffer (24) and Goldstein (25), while Peter's (26) case developed the lesions during his convalescence. Many writers, of whom DaCosta (27), and Hutinel and de Gimard (28) may be taken as fair samples, speak of measley and of scarlatinoid eruptions. Schamberg's (29) article gives an excellent summary of these conditions. In a study of 1500 cases of typhoid at the Johns Hopkins Hospital McCrae (30) notes erythema as occurring 15 times, urticaria twice, purpura 38 times and a pemphigoid eruption once. Thus it will be seen that true cases of erythema multiforme in the course of typhoid are very few.

J. B., a school boy, 14 years of age, a mulatto, was admitted to Freedmen's Hospital on November 5, 1909, complaining of a burning feeling in his eyes, severe headache, great weakness, bleeding from his nose, and a slight cough.

His family history was unimportant, his father, mother and two brothers having died of unknown causes, and his remaining brothers and sisters being in good health.

The patient had suffered from measles, mumps, malaria, and rheumatism, but from no other complaints, though he had had some vague indigestion, and some abdominal pain at night. He was accustomed to drink coffee and a little beer and whiskey, but otherwise his habits were good.

The present illness began two days before admission with a severe headache, which disappeared shortly to be replaced by a burning sensation about his eyes. He was so weak that he had to take to his bed at once. On the following day he had a severe chill, and in the evening nose-bleed. There was some slight cough.

On admission to the hospital the following notes were made:

"The patient is a well-built, well-nourished boy; the facial expression is dull and heavy; the pupils are equal and react to light and accommodation. The tongue is covered with a heavy fur; the pulse is 108 to the minute, regular in force and rythm, of good volume and tension. The chest is well formed and symmetrical; the breathing costo-abdominal in type, 28 to the minute. On percussion and auscultation both lungs are clear throughout. The heart is not enlarged to either the right or the left. The heart sounds are clear and forcible. The abdomen is not distended, it is everywhere soft and tympanitic, the liver is not enlarged, but the edge of the spleen is felt two fingers' breadth below the costal margin. The knee jerks are present."

On admission the temperature was 103° F., and during the illness ran between 100.8° and 103.8° F., the pulse from 80 to 115, and the respirations from 25 to 30. Typhoid was suspected because of the history and initial symptoms, the continued high fever, and the facies. The patient was given an initial purge, and was put on six ounces of milk every four hours, alternating with albumin every four hours. An ice cap was put to the head

and he was sponged every three hours when the temperature rose to 102.5° F., or higher. An enema was given every second day. Six ounces of water were given every two hours. Typhoid isolation was carried out.

Two days after admission the following note was made: "The patient shows over the back of his right hand and extensor surfaces of forearms a number of roughly circular, bluish patches about ½ cm. in diameter. Careful examination shows no rash on any part of the body with the exception of a few small rose-colored patches on abdomen and lower chest that disappear on pressure." Later in the day the following special note on the skin condition was made: "On the hands and forearms, both surfaces, extending half way to the elbow, the fingers, the dorsal surfaces of the feet and the shins there are two varieties of lesions, one of which is macular, ill-defined and varying in size from ½ to 3 cm. in diameter. The other lesion is distinctly annular, from ½ to 2 cm. in diameter, the center is red and the periphery is whitish. The edge is very well defined. On the extensor surfaces of both forearms there are scattered areas or spots that are free from pigment but having a hyperpigmented areola. The proximal finger joints seem slightly swollen, and are bright red in color, the general appearance being similar to the erythematous areas on the arms and legs." It was later found that the patient had suffered every spring for the last four years from an eruption that he described as being similar to the present one save that the lesions became vesicular and burst, leaving these white scars.

The urine had a specific gravity of 1026, and showed a trace of albumin but no casts nor red blood cells. The leucocytes numbered 4400, and a differential count of 500 cells gave:

Polymorphonuclears	66.6%
Eosinophiles	0.4%
Large mononuclears	1.0%
Small mononuclears	29.6%
Transitionals	2.4%

No mastcells or myelocytes.

The Gruber-Widal reaction, 1 to 50 for one hour, was negative. The blood pressure was 110.

On the 9th, two days after the last note, the carpo-phalangeal joints of both hands were red and swollen, and there were a few reddish macules on the proximal phalanges: the annular lesions still persisted on the forearms and backs of the hands and on the feet.

On the 19th there remained only a few annular lesions on both hands and feet. The temperature had now been normal for five days. He left the hospital on the 30th, with the same annular lesions still persisting. Blood cultures and cultures taken from the annular lesions were alike sterile. A Widal reaction, tried just before he left, was noted as suggestive.

Owing to the short duration of the fever, the absence of the Widal reaction, and the marked cutaneous symptoms it was questionable whether the patient was suffering from typhoid fever complicated by erythema multiforme, or from one of the severe forms of erythema with enlargement of the spleen, joint symptoms and continued high fever. In favor of typhoid were the continued high fever, the mental dulness, the coated tongue, and the low leucocyte count. Against typhoid spoke the abrupt onset, and the short duration of the fever, the absence of the Widal reaction and the negative blood culture, although the latter was taken rather late. The other symptoms and physical signs, including the differential count, could have occurred with either disease. A definite diagnosis was not made.

On December 6, one week after his discharge, the patient was again admitted to the hospital. His temperature was 103.6° F., pulse 110, and respiration 30. On the 7th the following note was made: "The patient looks dull and heavy, he complains of headache and pain in his eyes, there is slight discharge from the nose; the patient is not disposed to look at the light. The upper lip is somewhat swollen. The tongue is furred and there is injection of the throat. The chest is negative with the exception of numerous sonorous râles heard during inspiration; these clear up quickly after coughing and are probably transmitted from the larger tubes. The heart sounds are clear. The spleen is easily palpable. There is a marked redness of the palms of the hands and of the heels. A few small rose-colored papules are visible over the various portions of the body. Wherever the patient makes pressure with any part of the body there is a marked erythema. The patient is coughing, and spitting up grayish, frothy, mucopurulent material."

The blood coagulation time, taken by Wright's tubes, was six minutes.

On the 8th the temperature was 104.8° F., pulse 110, and respiration 33. The Widal reaction at one to fifty for one hour was suggestive. A blood culture was taken and an organism found whose cultural characteristics agreed with those of the typhoid bacillus, and which was definitely agglutinated by the serum from a known case of typhoid fever. This made the diagnosis of typhoid fever certain.

On the 10th the leucocyte count was 5700, the red blood cells 4,104,000 and the hæmoglobin 62%. A differential count of 500 cells gave the following results:

Polymorphonuclears	65.2%
Eosinophiles	0.6%
Large mononuclears	.6%
Small mononuclears	25.8%
Transitionals	3.4%
Mastcells	0.0%
Myelocytes	0.4%

The urine showed a large amount of albumin; no casts or red blood cells were noted.

The course of this attack was much more severe, the temperature running as high as 105° F. The treatment was the same as during the first attack with the addition of a mild expectorant for the cough. On the 9th it was noted that the patient was having bloody expectoration. On the 18th he had a rather free epistaxis in the morning and also coughed up a considerable amount of blood, which might of course have come from the nose. On percussion the lungs were clear throughout, but on auscultation there were numerous sibilant râles at the bases, both front and back. Over the chest, abdomen and back there were some pinkish macules about 1 mm. in diameter, and a few other papules that resembled acne lesions. There were no new lesions of erythema multiforme, but the old annular lesions still persisted.

On the 22d of December it was noted that the patient had had a sudden rise of temperature, the temperature previously having fallen almost to normal. Examination showed dulness in the lower right axilla, and impairment of expansion over the same area. Over the right base in front, and over the whole back there were numerous sibilant râles at the end of inspiration. There was no alteration of the breath sounds. These physical signs were similar to those usually found in pneumonia accompanying typhoid.

On the following day the temperature again dropped, and after the 29th there was no fever. Three weeks later the patient was discharged. He still had the annular lesions on the hands and feet, but they were now fading. The same annular lesions persisted from the 7th of November to the 22d of January, 1910, an unusually long time for the annular lesions of erythema multiforme.

It is certain that the patient had typhoid during his second stay in the hospital, and practically certain that he also was

suffering from the same disease during his first admission. During the height of his first attack he had the following symptoms characteristic of the erythemas: annular and macular skin lesions, and swelling and redness of the carpo-phalangeal joints. During the height of his relapse he suffered from œdema of the upper lip (giant urticaria), erythema at points of pressure, and hemoptysis. The fact that these lesions occurred only when the infection was young and active would seem to indicate that the typhoid toxemia was responsible for them.

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ACUTE TUBERCULOUS ENDAORTITIS.*

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The present consensus of opinion is to the effect that tubercle bacilli cannot, except in the rarest instances, be observed in the circulating blood. Yet we know that they must be present there and often in large numbers. We have built up our ideas of the production of miliary tuberculosis upon the assumption that the organisms that cause the disease are distributed by the blood, to which they gain access in three ways; by rupture of a tuberculous focus in one or another organ into a blood vessel; by the invasion of the walls of blood vessels, especially veins, by the tuberculous process, with the production of a tuberculous lesion in the intima of the vessel from which bacilli are distributed; and by the involvement of the thoracic duct in a tuberculous process, from foci in which tubercle bacilli gain access to the venous blood.

Vascular involvement is frequent, and it is probable that a search in every case of miliary tuberculosis will be rewarded by finding a focus of extension, most frequently in the smaller pulmonary veins, or thoracic duct, less frequently in the renal or pulmonary arteries, aorta, or the vessels of one or another organ of the body.

Invasion *per extensionem* is the rule in small vessels. It is not so common in large ones, nor indeed is vascular involvement of any sort. This invasive process is the one that usually accounts for the production of a generalized tuberculosis. It is the process by which the bacilli gain entrance to the blood stream, whence they are distributed. But there is a second process by which the secondary vascular lesions are produced. It may be assumed to occur generally as the result of thrombosis of, or endothelial phagocytosis in the capillaries of the tissues. As a result of either the vessel wall is involved from the side of the intima. This invasion from the lumen is frequent in small vessels but is infrequent in large ones for obvious reasons. It is least common in the aorta.

A review of the literature on tuberculosis reveals the fact that aortic lesions may be of the invasive or of the metastatic type, and that both are rare. The metastatic lesions may be acute or chronic in character.

In the cases of Dittrich and Kamen the aorta was involved from adherent tuberculous bronchial glands, and this was followed by acute miliary tuberculosis and rupture of the aorta (Kamen). In Buttermilch's case the aortic involvement was secondary to a vertebral tuberculosis.

Schmorl mentions two cases of acute miliary tuberculosis which he conceives as being the result of the perforation of a tuberculous lymph gland or of a pulmonary cavern into the aorta.

Examples of tuberculous aortitis by extension are the cases of Dittrich, Kamen, Schmorl, Hanau and Sigg, and Buttermilch. In the case of Hanau and Sigg an aneurism ruptured

* Read before the Cincinnati Society of Medical Research, October 6, 1910.

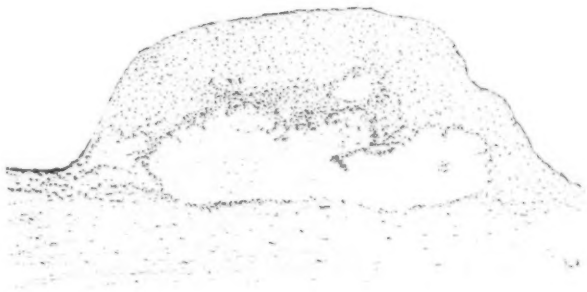

FIG. 1.

FIG. 2.

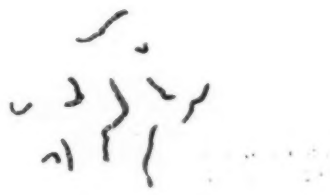

FIG. 3.

into a cavern in the lung. It is entirely probable that the aorta was weakened, its walls infiltrated and an aneurism caused thereby, after which rupture occured, for the edges of the torn wall of the aneurismal sac showed tuberculous vegetations.

The chronic type of tuberculous endaortitis is illustrated by the cases of Forssner, Benda, Aschoff, Longcope, Schmorl, Gaylord, Simnitsky and Luksch.

In this series there has been, with few exceptions, a more or less severe arteritis or arteriosclerosis in association with the tuberculous changes, a coincidence that has lead to the assumption that the specific lesions have been the result of invasion of parietal thrombi by tubercle bacilli. In them the process has apparently shown no tendency to advance along the intima, so that the lesions have increased into the lumen producing either flattened nodules or, more commonly, polypoid growths. In all the cases reported by Benda the lesions were polypoid. In two cases they were situated upon areas of sclerosis, in a third upon an atheromatous ulcer. In Luksch's case the lesions in the aorta, anonyma, and left subclavian were upon an endarteritic basis. In Forssner's case there was no arteriosclerotic change, but it is possible that in this the lesion was primary in the media resulting from a primary involvement of one of the vasa vasorum. The intimal tubercle measured 4 x 1 cm. Stroebes' case was one of a child in which there was a polypoid growth 7 mm. high and 3-4 mm. thick, with no arteriosclerosis. Aschoff's case showed extreme arteriosclerosis and a tuberculous mass the size of a bean near the origin of the Ductus Botalli. The lesion described by Longcope was a polyp 3 cm. long, which was found in the descending aorta of a child suffering from tuberculous hip disease. The report of Simnitsky, to which I have not had access, save through Forssner's paper, concerned itself with a case of chronic pulmonary and intestinal tuberculosis, and no miliary tuberculosis. The aortic lesion was in one of the sinuses of Valsalva.

In all of Schmorl's five cases there was arteriosclerosis, and in all the cases the tuberculous polypi were situated upon atheromatous ulcers.

Accordingly it appears that in this chronic group arteriosclerosis is more frequently present than is natural in tuberculosis, a disease in which the arterial tree is not as a rule severely affected, and it is therefore quite possible that the conception that the aortic lesions are the result of infection of mural thrombi is correct in the majority of cases. Ten of fourteen of the reported cases showed the presence of arteriosclerosis. In two cases I have not been able to find a description of the general aortic condition (Gaylord and Simnitsky) and in two the patients were young individuals (Longcope and Stroebe). In this enumeration Forssner's case is excepted since it is possibly in a class by itself.

The series of acute tuberculous endaortitis include the cases of Marchand, Huber, Schuchardt, Hanot, Hanot and Levi, Simnitsky, Blumer, Flexner and the one to be reported in this paper. In all of these miliary tubercles were present in the intima of the aorta.

The cases of Marchand and Huber were merely mentioned by Weigert who described them as showing the most exquisite structure, "giant cells, caseated center, etc." Schuchardt reported minute lesions situated near the junction of the thoracic and abdominal aorta. There was very little arteriosclerosis. I have been unable to find the report of the cases of Hanot and Simnitsky. That of Hanot and Levy was one in which a tubercle was found in the superior portion of the thoracic aorta. The tubercle discovered by Flexner was situated about 2.5 cm. below the left subclavian artery, and measured 2.5 x 1 mm. in diameter. The aorta was not sclerotic. Flexner believed that this tubercle was secondary to an infective thrombus in the pulmonary artery.

In all of the cases, of either acute or chronic type, the lesions have been described as containing large numbers of tubercle bacilli, a fact that has an important bearing upon the manner of the production of the general miliary tuberculosis that has been present in all except Simnitsky's first case, for many writers believe that the general lesions are the result of the escape of bacilli from the aortic lesions. It would seem reasonable, however, to limit the production of secondary general disease to the chronic cases, for in the acute ones the aortic lesions seem rather to be a part than the cause of it.

The case that I wish to report falls in the category of acute tuberculous endaortitides.

CASE 152173.—The patient, a man of 59 years, and a laborer, was admitted to the Cincinnati Hospital on November 11, 1909, complaining of "bladder trouble." In August, 1909, he had been admitted to a hospital for cystitis, which was improved by treatment with urotropin and irrigations. He had suffered with "bladder trouble" for some two years previously, that is to say, he had had pain on micturition, a symptom which was not constant, but which occurred in exacerbations, at the onset of each of which he passed some blood. At the time of his last admission he gave no evidence of pulmonary or cardio-vascular disease, except a slight roughening of the breath sounds during expiration. There was no splenic or hepatic enlargement. He suffered with involuntary urination accompanied by pain. The urine was dark red and contained blood clots.

A week after admission he had a convulsion at 9 p. m., accompanied by a rise of temperature to 102° F., and complained of pain radiating from the bladder to the renal region. There was pain and tenderness in left lumbar region. Subsequently the temperature showed an evening rise. Blood examinations showed a leucopenia, the counts varying from 4400 to 7800. A cystoscopic examination showed that there was a severe cystitis present. The capacity of the bladder was but 90 cc. A diagnosis of "cystitis, probably tuberculous, secondary to tuberculosis of kidney," was made. On December 10, complaint was made of abdominal pain, and on December 12 death occurred. The post mortem was made three hours after death.

Briefly stated the result of the autopsy was that a generalized acute miliary tuberculosis involving the lungs, spleen, liver, peribronchial and mesenteric lymph glands, kidneys, adrenals, pancreas and aorta was found. The bladder and kidneys showed both chronic and acute tuberculous changes.

In the thoracic part of the aorta there were a few fatty streaks, and at the beginning of the descending arch there was one calcified plaque. The abdominal aorta showed an almost completely healthy appearance except at a point 10-15 cm. above the bifurcation, at which point were two small raised areas on the intima

that had the appearance of recent vegetations and which measured about a millimeter in diameter. There was no tuberculous focus in the vicinity of the aorta in the neighborhood of these nodules.

Microscopic examination of the vegetation-like nodules in the aorta showed that they were really intimal tubercles, composed of epithelioid and small round cells, a partial endothelial covering, and a central area of caseation. In them were large numbers of acid fast rods of typical and atypical form, but no giant cells. Beneath these tubercles the media and adventitia were apparently normal, except immediately in the base of the tubercles where there was evidence of a minimal degree of degeneration in the adjacent part of the media.

In the lesions I have studied the bacilli were more numerous in the peripheral parts, and several were observed in the immediate vicinity of the lumen of the vessel. It is possible that some had entered the blood stream, but not in sufficient numbers to cause the appearance of the myriad lesions in other organs.

A further observation of some interest relates to the form of the bacilli in the intimal tubercles. In the cases in the literature, I have not been able to find reference to any other then presumably typical rods. In my case, however, many of the rods were far from typical. Quite a large proportion were of irregular form, and while no actually branching ones could be found, some of them showed bizarre figures that suggested branching.

I believe that in this case the generalized miliary tuberculosis, of which the aortic lesions were a part, was the result of distribution of the organism from the older foci in the kidney, and that it did not result from distribution of tubercle bacilli from the aortic tubercles. The case therefore belongs logically with the group of acute hematogenous aortitides.

It is difficult to account for the lodgment of the organism in these acute cases unless one presupposes at least an incipient degeneration of the cells of the intima, and the formation of ever-so little fibrin in which the bacilli may become entangled. It is very possible that in all cases of general infection and toxemia, more damage is done to the endothelial lining of the blood vessels than we can readily appreciate, a possibility which Baldassari has shown to exist by his observations on the endocardium in cases of infection and intoxication. Certainly it seems simpler to look at the process in this way than to suspect that normal endothelial cells in the aorta are fortunate enough to be able to seize single organisms from the rapidly flowing stream of blood that passes them.

Conclusions.

1. The case here reported is the eleventh of acute tuberculous endaortitis.

2. The aortic tubercles were the result not of extension, but of metastasis from chronic lesions in the kidney.

3. The general miliary tuberculosis that co-existed with the chronic tuberculosis, was not the result of dissemination of organisms from the aortic lesions.

4. The bacilli in the aortic lesions showed bizarre forms with a tendency to branching.

ILLUSTRATIONS.

Fig. 1.—Intimal tubercle. Drawn with camera lucida to show the general microscopic appearance.

Fig. 2.—An edge of the intimal tubercle showing the finer structure of the nodule.

Fig. 3.—Examples of acid fast bacilli showing bizarre shapes.

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REPORT OF A CASE OF EXTENSIVE TIERSCH SKIN GRAFT.

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(From the Clinic of Professor W. S. Halsted.)

The case herewith reported has two points of chief interest: the large size of the area grafted, and the demonstration by repeated trials, that only homografts would take in this patient.

Clinical History.

J. C., colored, was admitted to the Johns Hopkins Hospital on November 21, 1909, for flame burns of the back and of the left forearm and hand which he had received fourteen hours before admission. The burn of the back was of the second degree, the others of the first. The photographs show the situation and extent of the former lesion. The area of this was 430 square inches. As the total area of the patient's body is about 2800 square inches, the burn occupied between a sixth and a seventh of his entire cutaneous area.

The patient recovered from the immediate effects of the injury rapidly and with very little general systemic disturbance. While the sloughs were separating the wounds were dressed with a single layer of dry gauze, which was left in place for periods of a week or more, and then changed after giving the patient a prolonged warm bath. Absorbent dressings, changed as often as necessary, were placed over the gauze. This dressing proved very clean and comfortable. In

PHOTOGRAPH TAKEN DEC. 13, 1910, JUST BEFORE THE APPLICATION OF THE FINAL GRAFT.

PHOTOGRAPH TAKEN AFTER HEALING WAS COMPLETE.

less than two weeks the burned surface was covered with healthy granulations. Now followed a long series of attempts to cover the large raw area with skin. These I shall summarize briefly.

On December 16, 1909, 130 "pinch" grafts of rather large size were cut from the patient's thighs and planted over the lower part of the burn. About 110 of these lived, and, together with the epithelium which spread from them, covered an area of very considerable extent.

On December 23, 1909, at the suggestion of Dr. John Staige Davis, the experiment of grafting amniotic membrane was tried, but the epithelium of this failed to take.

On March 1, 1910, and again on March 18, 1910, large numbers of small whole-thickness grafts, obtained from two cases of lipectomy performed by Dr. Kelly, were applied, but these also were all unsuccessful.

On April 1, 1910, several large Tiersch grafts, cut from the patient's thigh, were spread over the granulations covering the right side of the chest. Most of this graft took, although the condition of the granulations was not so good as when the last two grafts were done.

On April 12, 1910, the granulations over the right scapula and the region immediately below were curetted away, and a large Tiersch graft, obtained from another patient, put over the curetted area. As had been the case with all the other isoplastic grafts, none of this lived.

No further attempts at grafting were then made for over five months. During this time the granulations became very deep and œdematous. In places they formed a gelatinous layer half an inch thick, the deeper parts of which were traversed by wide venous sinuses. About one-third of the total burn had now been covered by grafts. It was obvious that before further grafting could be done the granulations must be got rid of. Therefore the patient was anæsthetized (October 25, 1910) and the granulations curetted away down to the fascia, the bleeding being controlled with dry gauze. The cautery was found to cause as much hemorrhage as the curette. The patient was allowed to recover from this severe operation, and the curetted area to cover with fresh granulations. Following this at three separate operations the entire lesion was successfully covered with Tiersch grafts cut from the back of the thighs, and the left arm. These operations were done on November 9, November 23, and December 13.

With but one exception all the grafts were applied to healthy granulations prepared by simple irrigation with salt solution. The skin from which the grafts were cut was prepared by scrubbing with soap and water which was rinsed off with alcohol, and the latter with sterile salt solution. Silver foil dressings, which were usually left in place for ten days, were used. These were covered by very heavy rolls of absorbent cotton and gauze, all held in place by a crinoline jacket.

At present, two months after the last graft was applied, the new skin is freely movable on the fascia beneath. There is no tendency to keloid formation. The mobility of the back is practically normal. The areas from which the grafts were cut are very darkly pigmented. This was true for a time of the grafts also, but the latter are gradually fading to the light chocolate color of the rest of the skin. The total area grafted, determined by tracing its boundaries on a piece of moist crinoline applied over it, is 212 square inches in extent.

None of the isografts applied to this patient lived, though applied under the same conditions as the homografts, practically all of which did so. Dr. J. S. Davis, who has reviewed the cases of skin grafting at the Johns Hopkins Hospital (The Johns Hopkins Hospital Reports, vol. XV, page 307), found that in 499 cases of homodermic Tiersch grafts there were but 13 failures, or 2 3-5 per cent, while in 42 cases of isodermic Tiersch grafts there were five failures or 12 per cent. It has been demonstrated that isografts of highly specialized tissues take far less readily than homografts.* The same is true, but to a less degree of skin grafts.

I desire to thank Mr. Ives and Mr. Fullerton, of the present fourth year medical class of the Johns Hopkins Medical School, for their careful daily dressings of this case for over three months.

*W. S. Halsted, Journal of Experimental Medicine, 1909, XI, 175.

TWO CASES OF CONGENITAL HÆMOLYTIC JAUNDICE WITH SPLENOMEGALY. OBSERVATIONS ON HÆMOLYTIC JAUNDICE.

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In 1900 Minkowski reported the history of a group of individuals belonging to one family, all of whom showed a remarkable syndrome characterised by chronic acholuric jaundice, splenomegaly and urobilinuria. The appearance of these symptoms could be traced through three generations affecting at least eight members of the family. The general health of these individuals was not essentially impaired and no important changes were observed in the blood.

Bettmann, in the same year, described a similar case in which the jaundice displayed marked variations in intensity, deepening after exercise, food, drink and excitement, especially anger, and also after exposure to cold. An experimental

hæmoglobinuria might be produced in this case by the application of cold.

Pick (1903) and von Kranhals (1904) reported like cases, the latter having observed a family of which nine members in three generations showed a chronic congenital splenomegalic jaundice. In all instances the stools were of normal color. The urine which was of a dark color, was free from albumen, blood and hæmoglobin; it showed constantly the presence of urobilin, but never of bile. The number of red corpuscles was below normal, 2,300,000 and 3,500,000 respectively, in the men, and, on one occasion, as low as 1,000,000 in one of the women. The hæmoglobin ranged between 55% and 65%. The red blood corpuscles were irregular in contour and varied in size from 6 to 10 μ. There were no nucleated reds but well marked polychromatophilia.

Minkowski was fortunate in obtaining a necropsy of one of his patients. No especial changes were found in the liver, and the bile passages were quite clear. A small pigment stone was found in the gall bladder. The spleen was enlarged, and microscopically there were simple hyperplasia and hyperæmia. The kidneys showed a brownish discoloration produced by a granular pigment deposit in the epithelial cells of the convoluted tubules. Not only did this pigment give an intense reaction for iron, but there was a large amount of material united with proteids which gave the reaction only after boiling with ammonium sulphide. From but one kidney about 0.95 grammes of pure iron was obtained. Similar pigmentation did not appear in any other organ.

Minkowski regarded the condition as dependent on an anomaly of the blood pigment transformation, perhaps consequent upon a primary change in the spleen.

The clinical picture was not a new one. Similar observations had been made before by Murchison (1883), Wilson (1890) and Le Gendre (1897), and the syndrome appears to be similar to the Chronic Simple Jaundice with Splenomegaly of Gilbert and the Chronic Infectious Jaundice of Hayem (1898). It was, however, Minkowski's observation and necropsy report that first brought this condition sharply before the medical world. During the seven years following Minkowski's original communication, a considerable number of similar observations found their way into the literature: Chauffard (1901); Barlow and Shaw (1902); Mason (1902); Widal and Ravaut (1902); Arkwright (1903); Lortat-Jacob and Sabaréanu (1904); Caporali (1905); Claus and Kalberlah (1906); Strauss (1906); Benjamin and Sluka (1907).

These cases seem to bear a striking resemblance one to another and suggest a common cause. The absence of evidence of hepatic disease and the existence of extensive siderosis, especially of the kidney, in some respects analogous to that seen in Addisonian anæmia, on which Hunter especially has insisted, point to an increased blood destruction as a primary cause of the disease—an hypothesis adopted by most of these authorities.

In 1907 Chauffard made an interesting contribution to the study of this syndrome by the discovery in a similar case, of a marked fragility of the red blood corpuscles on exposure to hypotonic solutions of sodium chloride according to the method of Vaquez and Ribierre. This observation he was able to confirm in two patients presenting a similar syndrome in the wards of his colleague Widal. Thus, while with the normal red blood corpuscles hæmolysis begins at .42%-.44%, and is complete at .32%, in these three cases the beginning and end of hæmolysis were respectively .62% and .36%, .66% and .34%, and .52% and .18%. The average size of the red blood corpuscles was somewhat diminished.

Widal and Philibert on further study, were unable to demonstrate the presence of any hæmolytic properties in the serum of their own patients, either with regard to their own corpuscles or those of other individuals. This fragility of the red blood corpuscles, so marked toward hypotonic salt solutions, was also evident in respect to other hæmolytic substances. The diminished resistance of the red blood corpuscles has been a constant feature in the considerable number of cases of this malady which have since then been reported.

A few months later Chauffard described another interesting hæmatological feature which he had observed in all cases of this disease which had come under his observation, namely: the presence, on vital staining of a peculiar basophilic granulation of the red blood corpuscles. Chauffard's first studies were made by staining freshly made and fixed smears of blood with Pappenheim's (pyronin and methyl-green) solution. Many of the red blood corpuscles which are of a slightly grayish color and barely visible, having lost their refractiveness with their hæmoglobin, show a fine granulation of a bright red color. These dots, generally arranged about the periphery, are sometimes scattered throughout the cells in the form of a definite granulation. The granular corpuscles are usually somewhat larger than their neighbors; they may be demonstrated well by the method of vital staining of Widal, Abrami and Brulé.

Four to six drops of blood are allowed to fall into a test tube containing 10 drops of a basic coloring matter which is quite isotonic and contains in addition oxalate of potassium to prevent the coagulation of the blood.

Oxalate of potassium, 20%, 2 cc.
Unna's polychrome methylene blue, 100 drops } $\Delta = -0.60$

The fresh corpuscles are allowed to remain for 10 to 20 minutes in contact with the solution, after which the mixture is centrifugalized, the supernatant fluid is removed, and the corpuscles drawn up with a pipette and placed upon slides upon which they are spread as an ordinary drop of blood; the covers are then dried and fixed by heat. Such preparations may be preserved indefinitely.

The distribution of the granules is irregular. Sometimes scattered, they are usually collected in groups of two and three. Sometimes they are arranged in the form of a wreath or crown at the periphery of the corpuscle; they are generally distributed in such a manner as to suggest filaments wound around within the cell and showing frequent varicosities; they are unequal in size and of irregular form. Not infrequently

this granular net-work is gathered together toward the periphery or near the centre of the cell in such a manner as to suggest grossly a nucleus.

Sabrazès has called these corpuscles "granulo-reticulo-filamentous." The apparent reticulum is very adherent to the red blood corpuscle. If a dried and stained specimen be washed with pure water the corpuscles lose their blue color, while the granular filamentous appearance remains. Indeed, in some cases the reticulum may be found outside the corpuscle, lying between other well preserved elements. Widal, Abrami and Brulé have thought that the polychromatophilia which is present to a certain extent in these cases, bears a close relation to the presence of granular corpuscles, but this does not appear to be an absolute rule.

It is exceedingly interesting to see how closely these observers agree in their descriptions of this granulation with the careful studies of Vaughan (1903). Although originally described by Pappenheim,* the first careful studies upon the vital staining of the red blood corpuscles were made by Vaughan, who found that this granulation was present in somewhat under 1% of the red blood corpuscles of normal individuals. In the newborn, where they are most frequent, the highest percentage with but one exception (7%) was 4%. In pernicious anæmia with active regeneration, they were found in great numbers (once as high as 18%). In congenital icterus with splenomegaly the percentage is usually over 10%, and figures as high as 40% have been reported. Chalier, however, in his excellent monograph, is inclined to regard these figures as excessive, asserting that he, himself, has never seen a percentage above 20. This granulation, it is needless to say, is quite distinct from the basophilic granulation of Grawitz and others. The granules are different in shape and arrangement and are not to be stained in the fixed specimen. They are, of course, quite distinct from the remarkable Schüffner's granules which appear with Romanovsky's stain in certain parasitiferous corpuscles in tertian and æstivo-autumnal malaria.

It is probable that this phenomenon is simply an indication of active blood regeneration (Vaughan, Ferrata), but there are apparently few conditions in which the frequency of these granular corpuscles compares with that in congenital jaundice—a fact which seems to give them a real diagnostic value.

These observations have been confirmed by a considerable number of observers, and the picture of this disease, which Chauffard has called hæmolytic jaundice, is sufficiently definite to be regarded as a distinct clinical entity.

The patient often belongs to a family other members of which have suffered from the same condition. Early in life, sometimes immediately after birth, but in other cases later, perhaps not until puberty, a jaundice appears. This jaundice is usually of a moderate degree varying from a pale lemon hue to a well marked golden yellow. It is remarkably variable, increasing often under physical effort or emotional excitement. The stools are of normal color or pleiochromic, especially under those conditions associated with increase in jaundice.

The urine is of rather high color, often of a brownish almost mahogany hue, but free from bile. Urobilin is usually demonstrable. The blood shows an anæmia of moderate degree, generally between 3,000,000 and 4,000,000 red corpuscles, although in one case a blood count of under 2,000,000 is reported. There is usually considerable anisocytosis, but little or no poikilocytosis. The average size of the corpuscles is sometimes rather below the normal, a point upon which Chauffard particularly has insisted. The color index is somewhat reduced. Polychromatophilia is usually well marked. On vital staining the granulation described by Pappenheim, Vaughan, Sabrazès, Chauffard and others is present in a large number of corpuscles. The percentage of granular elements is usually above 10% and may be as high as 20%, or even more. The serum is of a clear, yellowish color, and the test for bilirubin is positive. Urobilin is generally undemonstrable. The leukocytes are usually of normal number or slightly increased. The differential count shows nothing remarkable beyond evidences of increased marrow activity as manifested by a high percentage of eosinophiles and the occasional presence of myelocytes and nucleated red cells—normoblasts.

The serum shows a rather high degree of hypertonicity. Starkiewicz regarded this condition as a mechanism of defense on the part of the organism to protect the fragile red corpuscles. Troisier, however, believes it to be the result of exosmosis of the corpuscular salts as a result of the fragility of the red cells.

The remarkable feature of this interesting condition is that subjective symptoms are usually absent despite the constant anæmia. The patients are generally unconscious of any disability. They appear to adapt themselves so well to their condition that it is only occasionally that a complaint is elicited. There is a complete absence of all the ordinary phenomena of biliary intoxication: there is no bradycardia; no pruritus; no tendency to hæmorrhage; no xanthelasma. The patients are, indeed, as Chauffard has gracefully said, "à peine des malades—plutôt des ictériques que des malades"—barely patients, rather icterics than patients.

There is one exception to this rule. Many of these individuals suffer from attacks of abdominal pain suggestive of biliary colic. These pains, localized in the epigastrium and in the region of the gall bladder, are often accompanied by fever and by an aggravation of the jaundice. In a number of instances they have been so severe as to lead to operation. In many cases it is probable that the attacks are due to the presence of small pigment stones in the gall bladder, such as have been found in four of the six cases of congenital jaundice that have come to necropsy—every instance but one in which the gall bladder was examined.

In the last several years the authors have had the opportunity of observing two striking cases of congenital hæmolytic jaundice which appear to be worthy a note of record.

* This subject is well discussed by Ferrata who, however, in common with every continental author, ignores Vaughan's excellent work.

CASE I.—Miss X., 16 years of age, a school girl, consulted one of us (W. S. T.) on the 30th of May, 1906, with a complaint of jaundice. Her father and mother were well and strong. She has one sister, younger than herself, who is perfectly well, and the family history in other respects, is good.

Her mother states that as an infant the patient used to have slight attacks of jaundice for which they were accustomed to give her calomel, but as she grew older the attacks became more frequent until, finally, the jaundice became permanent. The yellow color has varied in intensity from time to time, but the mother is not sure that it has ever been wholly absent. It has been deeper as a rule at the time of menstruation, and worse after exertion and bad colds, or with any indisposition. Six years ago the patient had a febrile attack which was regarded as typhoid fever. In other respects she has been a strong healthy girl, taking part in all the out-of-door games of her companions. She is not conscious of having been short of breath.

Eight months ago she began to have occasional attacks of pain in the right side of the epigastrium, lasting from ten to twenty minutes. Of these attacks she has had several. Three weeks ago she had a paroxysm of sharp, cramp-like pains in the same position, so sharp that at times while at school she had to lie down; there has been no fever with any of these attacks, but in the last three weeks she has had more or less pain, usually every other day. Lately the jaundice has been worse, but it is the pain that has excited the attention of her parents.

In other respects she had felt perfectly well and only recently, since she has grown older, she has been somewhat annoyed by the consciousness of her jaundice.

On examination there was a distinct jaundice although in other respects the color of the patient was that of a healthy girl; the tongue was clean; pulse 19 to the quarter, regular, not remarkable. Examination of heart and lungs negative.

Abdomen, natural; no tenderness on pressure in the region of the gall bladder; palpation, negative, although, on light percussion, there is possibly a very slight suggestion of dulness in the region of the gall bladder. The spleen is readily palpable, descending on deep inspiration at least 4 cm. below the costal margin.

Widal reaction, negative.

Blood:

R. b. c.	3,680,000
W. b. c.	800,500 ← ?
Hb.	70-71%

Dried and stained specimens showed the red blood corpuscles of about normal size with but slight variation in diameter; the color is good; no marked polychromatophilia. Their contour is fairly regular, but there is some distortion, a few elliptical and dumbell shapes being found. No nucleated reds.

Differential count:

Polymorphonuclear neutrophiles	72.5 %
Small mononuclears	18.0%
Large mononuclears	7.5 %
Transitionals	1.5 %
Eosinophiles	.5 %

The case was regarded as one of chronic, congenital jaundice with splenomegaly of the type described by Minkowsky. There was a question as to the existence of gall stones, but, in the absence of severe symptoms, operation was not advised. Blaud's pills to be continued through long periods of time, were prescribed.

Three years later, having become familiar with the work of Chauffard, Widal and others, the writer requested the parents of the patient to allow him to see her again. She was accordingly seen on the 20th of March, 1909. Jaundice had been present for the greater part of the preceding three years, although the patient had grown and developed normally and was a perfectly healthy looking girl. The mother says that after long periods in the house she becomes more jaundiced and that dancing, violent exercise and bad colds make it worse. It is worse at the catamenial periods, better just afterwards. The author's note on this occasion reads:

"Strong, healthy looking girl; color good; tongue clean. There is a distinct slight jaundice of the skin and conjunctiva. Pulse 22 to the quarter, regular, not remarkable in quality. Heart sounds, clear at the apex and base.

Abdomen: natural in appearance. Spleen, readily felt just below the costal margin, descending on deep breath 3 or 4 cm. below. It seems smaller than when last seen. The liver descends just below the costal margin on deep breathing; flatness above at about the 6th rib, extending to the costal margin. Gall bladder, not felt.

Blood:

R. b. c.	3,200,000
Hb.	75%

Resistance of the red blood cells: 1 cc. of blood was collected in 9 cc. of 1% aqueous sodium fluoride solution, and the corpuscles were subsequently washed three times in 0.85% NaCl solution. A 5% suspension of the red corpuscles in 0.85% salt solution was prepared. The corpuscles were then placed in solutions of NaCl of varying strength and the first trace of hæmolysis (minimal resistance) and complete hæmolysis (maximal resistance) noted. The results showed:

Minimal resistance	0.68% NaCl.
Maximal resistance	0.45% "

After centrifugalizing the blood-sodium fluoride mixture, the supernatant fluid was found to be of a canary yellow color; it was pipetted off and tested for urobilin and bilirubin. Neither pigment could be demonstrated, using the technique described by Conner and Roper.

Urine.—Fresh specimen March 20, 1909. Brownish yellow, clear, acid, sp. gr. 1.014; albumen and sugar absent; bile: foam white; tests with yellow nitric acid negative. Trousseau's test (tincture of iodine) negative. Urobilin: marked green fluorescence on treating the amylic alcohol extract with 1% $ZnCl_2$ in ammoniacal alcohol; also positive on spectroscopic examination.

On the 4th of April, after taking Blaud's pills gr. V, t. i. d. for two weeks, the patient allowed us to make another examination of the blood:

R. b. c.	3,800,000
W. b. c.	5,200
Hb.	84% (Dare.)

Vital staining of fresh blood with Unna's polychrome methylene blue, according to the method of Vaughan, showed 149 red cells with basophilic granulations out of 1228 cells examined, or about 12.1% (normal = 0.5% to 1.8%.—Vaughan).

Differential count of 564 cells with Ehrlich's triacid stain:

Lymphocytes	18.6%
Large mononuclears and transitionals	3.5%
Polymorphonuclears, neutrophilic	73.0%
Polymorphonuclears, eosinophilic	1.2%
Polymorphonuclears, basophilic	0.7%
Myelocyte, neutrophilic	0.17%
Degenerated	2.6%

Wilson's stain (Romanovsky) and the triacid stain were used in studying the red cells. There was moderate anisocytosis, no poikilocytosis. The red cells were of good color and no polychromatophilia, basophilic granules, nuclear particles, Cabot's ring

bodies, or nucleated reds were seen. The blood platelets were rather few in number in the stained specimens.

Resistance of the red blood corpuscles:

Minimal resistance	0.72% NaCl.
Maximal resistance	0.42% "

The blood plasma-sodium fluoride mixture was again of a brilliant canary yellow color. Using the methods recommended by Conner and Roper, bilirubin was demonstrated; tests for urobilin were negative.

Urine.—Fresh specimen, April 8, 1909. Yellowish brown, clear, acid, sp. gr. 1.024; albumen, sugar and bile, absent. Urobilin: marked positive reaction, both chemical and spectroscopic. Microscopical examination showed a few squamous epithelial cells; otherwise negative.

Stool.—Dark brown, small, constipated stool. No blood, pus or mucus. Microscopical examination: a few muscle fibers without striations, many yeast cells. No ova or parasites. Schmidt's test (concentrated corrosive sublimate) positive for urobilin, negative for bilirubin.

Blood.—The average diameter of 500 red corpuscles in dried and stained specimens (Wilson's modification of Romanovsky) was 7.45 μ. The variations were between 5 and 9.4 μ—essentially normal measurements.

In July of the same year the patient was seen in Europe. At that time she seemed perfectly well but showed, as always, a distinct slight jaundice of the skin and conjunctivæ.

The general appearance of the patient was very remarkable. Without observation one would have picked her out as a perfectly healthy girl; her cheeks were red and her expression bright, the general nourishment good and it was a matter of great surprise to find so marked an anæmia. She had never been short of breath and complained of no subjective symptoms of anæmia.

The second case was seen in the wards of Prof. Barker, to whose courtesy we are indebted for the privilege of reporting the case.

CASE II. (Med. No. 23623).—F. B., single, age 27, a manicurist, was admitted to the hospital on January 22, 1909, complaining of jaundice. The family and personal history are good. No other member of the family is jaundiced. The patient has had measles at 9, mumps at the same age and whooping-cough at 12. During the last twelve years there have been occasional attacks of major hysteria, usually following mental shock. There has been chronic constipation. The patient has been jaundiced since she was three days old; the jaundice is variable, sometimes very deep and again scarcely noticable. Since the age of 16 she has complained of what she called bilious spells about twice a month. While dressing in the morning she becomes nauseated, vomiting one or two ounces of fluid, at first like water and then almost pure bile. A few minutes after vomiting she feels relieved and is able to go to work.

There is no history of pain in the region of the gall bladder, or of hæmatemesis. The patient has not passed acholic or bloody stools to her knowledge. She has had no abdominal pain. In July cholecystostomy was performed by Dr. John D. Blake. No gall stones were found.

About two months ago the patient began to have a "dead, aching pain" a little below the right scapula; the pain seldom shifted. There has been slight pain occasionally above the left nipple. Her average weight is 138 lbs.; in the last three months she has lost 13 lbs.

Status presens. (Dr. Boggs).—The patient is well nourished. There is a marked icteric tint to the entire skin, the scleræ and the mucous membranes. No xanthoma. The lungs are negative. Heart: Apex is just felt in the 4th interspace 9.5 cm. to the left of the median line. Relative cardiac dulness extends 10.5 cm. to the left in the 5th, 3.5 cm. to the right in the 3rd interspace, and above to the 3d rib. There is a soft systolic blow at the apex, transmitted to the axilla. Pulmonic second sound accentuated. There is a blowing systolic murmur over the conus.

Abdomen: Spleen extends 4 cm. downward and forward beyond the costal margin. Liver not palpable. No hæmorrhages noted.

Jan. 29. (Dr. Thayer). Perfectly healthy looking woman with yellowish type of jaundice. Tongue clean. Abdomen slightly more prominent on left. Spleen readily palpable. Liver not enlarged.

Feb. 5. (Dr. Hanes). Since admission the patient's only complaint, jaundice, has varied very markedly from a light yellow to a deep lemon color. The scleræ are constantly yellow and do not vary as much as the skin. The heart is as noted before,—the systolic blow is very faint and is not transmitted to the axilla. Spleen still enlarged, edge firm and sharp. Patient discharged.

During the patient's stay in the hospital, her blood pressure (systolic) varied between 100 and 118 mm. Hg. The temperature was between 97.6° and 100.2° F. Pulse 60 to 83, respirations 18 to 20.

Blood examinations:

Jan. 23.	R. b. c.	3,800,000
	W. b. c.	8,900
	Hb.	70%

In the fresh blood the red cells appear normal in color and shape. No nucleated reds or parasites.

Jan. 26. Wasserman reaction negative. Coagulation time, 5 min.

Jan. 27. Blood count practically the same as on the 23d.

Jan. 28. (Dr. Hanes). The patient's blood serum is of a golden yellow color, and the HNO_3 test for bile is positive.

Jan. 29. (Dr. Rous). "Resistance of the red blood cells to hypotonic salt solution. Into a series of tubes containing 1 cc. each of dilute salt solution 20 mm. of the patient's whole blood were dropped. The dilutions comprised a series from 0.85% to 0.10% NaCl. As control, the blood of S., who had about the same number of cells per cm., was taken. The corpuscles of S. showed complete hæmolysis at a dilution of 0.30% and those of the patient at 0.40%. (This is an immediate observation). After 24 hours the reading showed a trace of hæmolysis at 0.55% for S., and about the same at 0.75% for the patient."

Differential count of 400 cells showed:

	Lymphocytes	47.0 %
	Large mononuclears and transitionals	5.25%
	Polymorphonuclear neutrophiles	46.0 %
	Polymorphonuclear eosinophiles	0.5 %
	Mast cells	0.25%
	Unclassified	0.75%
Feb. 3.	R. b. c.	3,700,000
	W. b. c.	10,500
	Hb.	76%

Viscosity 4.1 (in terms of distilled water).

Stool examinations were made on Jan. 27 and 29 and on Feb. 3. Schmidt's test showed only hydrobilirubin. Microscopically nothing of importance was found.

Urine was examined on six different days. Sp. gr. 1.018 to 1.030. There was no albumin or sugar. No bile or bilirubin was demonstrated. Urobilin was tested for apparently only on Feb. 4th, when the report says, "Schlesinger's urobilin test negative. Spectroscopic examination inconclusive." The color of the urine was described as brownish yellow and orange.

It is rather unfortunate that more careful tests for urobilin were not made; it must have been present.

All attempts to communicate with the patient since her discharge from the hospital have failed.

These cases are typical examples of this condition. Although both patients showed a well-marked jaundice, in neither was there the slightest disturbance in the shape of itching; in neither was there bradycardia. The complaint of the second patient bore apparently no relation to her jaundice. The extraordinary manner in which these individuals adapt themselves, as it were, to their anæmia, is strikingly illustrated by both of our patients, especially by the first, whose appearance and history were not of a delicate but rather of a robust, strong girl.

A striking peculiarity in the observations made upon this case is the remarkably high point of concentration of the solutions of sodium chloride at which complete hæmolysis appears, .42% and .45%, a concentration equal to or above that at which, in the normal individual, hæmolysis begins.

Acquired Hæmolytic Jaundice.—This remarkable syndrome, chronic acholuric pleiochromic jaundice without the usual symptoms of biliary intoxication, associated with anæmia, enlarged spleen, and siderosis of the viscera is not, however, always of congenital origin. Soon after Chauffard's first observations, Widal and Abrami, Chauffard and Troisier, Le Gendre and Brulé, von Stejskal, Oettinger, Parkes-Weber and others reported a series of interesting observations in which a similar train of symptoms came on without apparent cause in adult life. The onset of the jaundice in these instances followed various different accidents—an ischio-rectal abcess (Widal and Abrami), hæmorrhage following a miscarriage (Widal and Abrami), severe nervous shock (Chauffard and Troisier), acute gastro-enteritis (Le Gendre and Brulé). In other instances, such as the two cases of von Stejskal, that of Oettinger, and that of Parkes-Weber, the process seems to have appeared without striking initial symptoms. Again, in a considerable group of cases a jaundice of a transient character presenting similar hæmatological phenomena—an anæmia with signs of regenerative activity of the bone marrow, granular corpuscles on vital staining and a marked fragility of the red cells, has been observed in the course of a variety of conditions, cancer of the stomach (Chalier); cirrhosis of the liver (Chalier and Le Play); malaria (Sacquépée, Chalier); repeated hæmorrhages in cancer of the bladder (Widal and Joltrain); streptococcus infection (Sacquépée); uncinariasis (Darré); syphilis (Gaucher and Giroux); pulmonary tuberculosis (Landouzy); jaundice of the new born (Sabrazès and Leuret; Cathala and Daunay).

This acquired hæmolytic jaundice, as it has been called by Widal and Abrami, who described the first cases, does not constitute a definite disease picture to the same extent as does congenital splenomegalic jaundice, but rather an interesting syndrome. Acquired hæmolytic jaundice may be divided, as suggested by Brulé, into apparently *primary* and *secondary* cases. The former arise either without apparent cause or during the course of some acute transient malady, after which they persist with seeming independence. Secondary hæmolytic jaundice is observed in a transient manner associated with acute infections or poisons, or as a terminal phenomenon in the course of some chronic disease.

One essential difference exists between most of the cases of acquired hæmolytic jaundice and the congenital malady, namely: the existence in the former of an anæmia sufficiently grave to occupy a prominent position in the clinical picture. The anæmia may, indeed, be intense and is associated with the usual subjective symptoms. There are often striking variations in the intensity of the jaundice and the grade of anæmia. Sudden paroxysms of fever associated with painful swelling of the spleen and extremely rapid fall in the number of red corpuscles have been described.

A patient of Widal and Abrami's showed, on the 19th of May, 2,600,000 red blood corpuscles; ten days later, while in apparently good condition, there appeared severe headache, dyspnœa, marked exacerbation of the jaundice, and in a day or two the blood count showed but 850,000 red elements. In one of von Stejskal's cases the blood count rose in eighty days from 640,000 to 4,000,000.

The blood picture is often very similar to that in pernicious anæmia; marked oligocythæmia; a high color index; anisocytosis; poikilocytosis; often an increase in the average corpuscular diameter. There are almost always marked evidences of marrow activity in the shape of nucleated red blood corpuscles, among which megaloblasts are often found. Contrary to what one sees in pernicious anæmia, the leukocytes are usually somewhat increased, and, occasionally, there is a well-marked leucocytosis, which, on differential count, shows a considerable proportion of myelocytes and a large percentage of eosinophiles. Granular corpuscles are present on vital staining, as in the congenital form of the disease; sometimes, however, these are not so numerous.

There are two striking points of difference in the hæmatological picture between acquired and congenital hæmolytic jaundice. The corpuscular fragility, so evident in the former condition, is often very slight in the acquired disease when the test is made with unwashed corpuscles.

Widal and Abrami showed early that in acquired hæmolytic jaundice the corpuscular fragility may, indeed, be almost inappreciable if the test be made with the whole blood. With deplasmatized corpuscles, however, the resistance is distinctly, sometimes very markedly, diminished. These authors showed that this increased fragility of the deplasmatized red corpuscles is common to both congenital and acquired varieties of the disease with the essential difference that while in congenital hæmolytic jaundice the fragility is usually demonstrable with the whole blood, in the acquired condition the resistance of the whole blood may be normal, while that of the deplasmatized corpuscles may show a very marked reduction. The deplasmatized red blood corpuscles of acquired hæmolytic jaundice show also a distinct diminution in resistance toward other hæmolytic substances, such as anti-human sera of all sorts and leech extract.

In normal blood the resistance of the deplasmatized corpuscles does not differ essentially from that of the whole blood.

While it is difficult to avoid the conclusion that this increased corpuscular fragility has a definite association with the hæmolysis which occurs in these cases, yet it should be

remembered that no direct parallelism can be drawn between the degree of fragility and the extent of the anæmia. The conditions existing in congenital and acquired hæmolytic jaundice form an interesting paradox, as has been pointed out by Brulé; on the one hand a marked corpuscular fragility associated with a moderate anæmia, on the other a moderate fragility and an intense anæmia. "It is impossible to draw a direct conclusion as to the fragility of the red blood corpuscles in the organism from their fragility in vitro."

This diminution in the resistance of the deplasmatized corpuscles may be restored if they be brought into contact again with their plasma. Although there is a slight difference between the resistance of the corpuscles according to the manner in which they are separated from their plasma (Iscovesco, Salignat), yet these differences are so slight that they need not be considered; in fact the quantity of serum necessary to restore the resistance of separated corpuscles is so large that, practically, it is unnecessary to wash the corpuscles deplasmatized in an oxalate solution. The anti-hæmolytic power of the serum is not restricted to that of the patient himself. It is present in other and heterologous sera. Heating to 56° C. for a considerable period of time does not remove the power. There would then appear to be no evidence of the existence of a specific anti-hæmolytic substance. Widal, Abrami and Brulé believe that the anti-hæmolytic power is dependent on some special physical property or properties of the serum.

The blood of some individuals with acquired hæmolytic jaundice possesses one characteristic which, for the moment, appears to be rather special, and is not observed in the congenital forms, namely, an auto-agglutinative power of the serum. The test is a relatively simple one; it is thus described by Brulé.

"One lets fall into a watch glass 10 drops of the patient's serum and then a drop of red blood corpuscles isolated by centrifugation: the mixture is shaken up and then allowed to rest. Soon the corpuscles are seen to gather at the bottom, sometimes appearing to form little masses. But if there is no auto-agglutination, we need but to shake the glass slightly to restore the mixture to its previous homogeneity and to disperse the corpuscles in the serum. If the auto-agglutination be positive, one sees after a period varying according to the intensity of the phenomenon, from one to twenty minutes, a collection of the corpuscles into little granules easily perceptible by the naked eye, which give the emulsion an aspect comparable to brick dust; violent and prolonged shaking cannot dissociate these corpuscles. Little by little the agglutination increases, the corpuscles gather at the bottom of the watch glass where they form an homogeneous pellicle, the supernatant serum becomes limpid, and shaking no longer dissociates the hæmatic pellicle. If at the beginning of the phenomenon one examines a drop of the serum microscopically it may be seen that the corpuscles, instead of disposing themselves in rouleaux as normally, gather in little islands, between which there float a few isolated corpuscles."

This phenomenon has been found in a number of instances of acquired hæmolytic jaundice. In others, such as the cases of Widal and Joltrain, and that of Parkes-Weber, auto-agglutination has been absent. The phenomenon is interesting and may be of considerable diagnostic value. It is not present in congenital hæmolytic jaundice, although the patient of Bénech and Sabrazès, whose jaundice is believed by the authors to have been acquired from a wet nurse, might be regarded as belonging to this class. It has, however, been observed in one instance of hepatogenous jaundice by Brulé. It should be said that it has not as yet been studied sufficiently to justify far-reaching conclusions as to its diagnostic value or significance.

Attacks of pain in the region of the gall bladder associated with fever and exacerbation of the jaundice are very common. Indeed, the first three reported cases (Widal and Abrami; Chauffard and Troisier) were all operated upon for suspected gall stones. In one of these cases a little bile sand was found; in the other instances the gall bladder was quite clear.

Acquired hæmolytic jaundice presents itself in a variety of forms. The most important are:

1. Those cases simulating cholelithiasis.
2. Those simulating pernicious anæmia with jaundice.
3. Those simulating a chronic infectious cholangitis, chronic, infectious, splenomegalic jaundice (Hayem).
4. It has also been observed in some of those conditions in which the most striking symptoms, anæmia and splenomegaly, leave one in doubt as to whether the case should be classed clinically as Banti's disease or a cirrhosis of Hanot's type. Recent studies by Chauffard and Troisier, as well as by Armand-Delille and Feuillé, suggest strongly the possible relationship between some so-called splenic anæmias and hæmolytic jaundice. Attention has also been called to this point by Parkes-Weber.

In other instances the condition may manifest itself under the symptoms of an *icterus gravis* (Roque and Chalier).

The syndrome is, however, sufficiently definite and easily to be recognized if carefully studied, by the absence of bile in the urine, its presence in the blood serum, the urobilinuria, the presence of a large percentage of granular corpuscles on vital staining, by the fragility of the red corpuscles, especially manifest with the deplasmatized elements, and by the commonly present auto-agglutinative power of the serum.

It is important to remember that in Addisonian anæmia and in cholelithiasis the corpuscular resistance is at least normal; indeed, as a rule, it appears to be increased. In one of my cases of pernicious anæmia hæmolysis began at only .325%, and was complete at .275%, a greatly increased resistance.

In obstructive jaundice Vaquez and Ribierre have also shown that the resistance of the red corpuscles is as a rule distinctly increased, an observation which we have been able to confirm.

Pathological Anatomy.—Several individuals presenting the syndrome of hæmolytic jaundice have come to necropsy (Vaquez, Giroux and Aubertin; Oettinger; Gandy and Brulé; Widal and Joltrain; Roque and Chalier; Micheli; Möller; Wilson; Tileston and Griffin). The cases of Vaquez, Giroux and Aubertin, Gandy and Brulé, Wilson, and Tileston and Griffin, were apparently of congenital origin; the others, probably acquired. In all cases, however, the essential features appear to have been general evidences of an hæmolytic process as

manifested by a siderosis of liver, spleen and kidneys. The autopsy in the case of Vaquez and Giroux is of especial interest as it occurred in a congenital case in which death followed splenectomy, so that complications with other terminal processes were ruled out. The lesions which have been confirmed in the later cases, were as follows:

A marked congestion of the spleen especially confined to the pulp, the engorgement of which was in rather striking contrast to the relative emptiness of the sinuses. There were few macrophages in the splenic pulp, more in the sinuses. The endothelial cells were stuffed with iron containing pigment.

The liver showed no evidence of biliary obstruction, no angio-cholitis. Many of the liver cells, especially in the centro-lobular zones, were, however, stuffed with large granules of ochre pigment.

There was moderate siderosis of the cells of the convoluted tubules of the kidney, and marked hyperplasia of the marrow.

These observations have been confirmed, in great part, in all cases which have come to necropsy, affording thus abundant evidence of the hæmolytic character of the process. The siderosis of the kidney, which is usually present, has, however, been very moderate in some instances, and was apparently absent in Gandy and Brulé's case of congenital hæmolytic jaundice, where death occurred in the course of a pneumonia as well as in Micheli's instance of the acquired form of the disease. In no instance was there evidence of biliary obstruction.

Pathogenesis.—The pathogenesis of this remarkable syndrome is by no means clear. The evidence of a chronic hæmolytic process is not so very different, indeed, from that which one sees in various other conditions, such especially as Addisonian or bothriocephalus anæmia, conditions in which chronic jaundice is not uncommon. The clinical picture in some of the acquired forms of the disease with crises of aggravation of the malady, may almost resemble paroxysmal hæmoglobinuria. Here, as Donath and Landsteiner have shown, there is in the serum a true auto-hæmolysin. But in paroxysmal hæmoglobinuria there is no evidence of a diminished resistance of the red blood corpuscles.* In Addisonian anæmia, as has already been said, the resistance of the red blood corpuscles is usually increased.

On the other hand there is no evidence of a specific hæmolysin in these instances of jaundice associated with corpuscular fragility, so that one has been tempted to separate an hæmolysinic jaundice, such as the jaundice with pernicious anæmia or that seen with paroxysmal hæmoglobinuria, from the jaundice associated with corpuscular fragility, to which the name *hæmolytic* has come to be applied—a deplorable complication of terms.

This is, however, not to say that the primary causal element in some of the instances of so-called acquired hæmolytic jaundice may not be the presence of toxic hæmolytic substances in the organism. Indeed, there is some reason to believe that this may be the case. Troisier, for instance, in his recent thesis advances various arguments in support of the hypothesis that the fragility of the red corpuscles in these cases of hæmolytic jaundice is dependent upon the fact that they have already become sensitized by union with an hæmolytic amboceptor.

However this may be, we are in the presence of a remarkable clinical syndrome—acholuric, pleiochromic, jaundice, anæmia, corpuscular fragility, granulation of the red corpuscles on vital staining, post-mortem evidences of blood destruction in the form of siderosis of the liver, spleen and kidneys, absence of evidence of the presence of hæmolytic substances in the serum.

Several questions naturally suggest themselves.

1. Where does the hæmolysis take place?

2. Where does the bilirubin circulating in the blood find its origin?

3. What is the primary cause of this condition?

1. As to the manner and seat of the hæmolysis there have been varying opinions. Some (Minkowski, Chauffard, Vaquez) fancy that, gathered in the pulp of the spleen which, as has been seen, is always markedly engorged, the abnormally fragile corpuscles are there destroyed. Others (Widal and his pupils) are inclined to believe that the destruction occurs in the general circulation, the débris accumulating as it always does in the spleen, and accounting thus for the symptoms and manifestations on the part of that organ. One observation, as pointed out by Castaigne, is strongly in favor of the circulatory origin of the hæmolysis, namely, the siderosis of the kidneys, which is often demonstrable. Otherwise no important evidence can be adduced in support of one or the other of these views which, in the end, are essentially the same, excepting in so far as they bear upon the second question.

2. *The Cause of the Jaundice.*—Most observers have believed the jaundice to be immediately hepatic in origin due to the over-production of bile by a liver overstocked, so to speak, with the products of blood destruction. The old idea that this was, in a sense, after all, an obstructive jaundice owing to the inspissation of the bile and the engorgement of the intra-hepatic bile passages, or to a diffuse intrahepatic cholangitis, must, however, be abandoned as a result of the clinical and pathological observations of some of these cases. If the hepatic origin of the jaundice be accepted, we must fall back upon the assumption of Minkowski, that the overworked hepatic cell gives off a part of the excess of bile which it produces into the capillaries, as well as into the bile passages.

Widal and his pupils, however, advance another hypothesis, which is in many ways inviting. Pointing out the rapidity with which jaundice follows experimental blood destruction in animals, they call attention to the lack of evidence of any inspissation of the bile, referring especially to one of their patients on whom a cholecystostomy was performed for suspected stone. The gall bladder and ducts were empty, and the bile which was discharged from the fistula in large quanti-

* It is true that Meyer and Emmerich believe that they have been able to demonstrate a diminished resistance of the red corpuscles in paroxysmal hæmoglobinuria against changes of temperature, dilute acids and saponin. Meyer and Emmerich: Ueber paroxysmale Hæmoglobinurie. Deutsches Arch. f. klin. Med., Leipsig, 1909, XCVI, 287-327.

ties, was of normal character, and strikingly fluid. On the other hand they observe that Langhans and Quincke have demonstrated bilirubin in the seat of old hæmorrhagic foci, that Sabrazès and Muratet have observed the presence of urobilin in cerebro-spinal fluid after cerebral hæmorrhage, and that Froin has shown that hæmoglobin may be changed into biliary pigment in hæmorrhagic exudates in the meninges and in the pleura, observations which have been confirmed by Guillain and Troisier, Widal and Joltrain and others. The urobilin which various observers have demonstrated in the serum they believe to be due to a direct transformation from hæmoglobin through bilirubin such as has been shown to occur in hæmorrhagic exudates (Troisier: Thèse). They point to the fact that in cases presenting the syndrome of which we have been speaking, despite the long-continued jaundice, there is no evidence of the ordinary symptoms of biliary retention, symptoms which they believe to be due to the action of biliary salts, namely, pruritus, bradycardia and emaciation. Bile acids have never been found in blood or urine. Nor do the red corpuscles show the increased size and heightened resistance to hypotonic salt solutions which Rist and Ribadeau-Dumas believe to indicate an acquired tolerance for intoxication by taurocholate of sodium. Everything, they think, points to the existence of a purely pigmentary cholæmia which, theoretically, might easily arise in the blood itself. This is a conceivable and seductive hypothesis. The objections based upon the absence of hæmoglobin in the circulation, which have been raised against this idea are answered by Widal by the assumption of a destruction of the corpuscles so gradual that the quantity of hæmoglobin is too small to be recognizable. It cannot be said, however, that the symptoms of ordinary biliary intoxication are never present, rare though they be, for itching has been observed in one or two instances. On the other hand the argument that the absence of these symptoms is evidence of the purely pigmentary character of the jaundice is based upon a false assumption, for King and Stewart have shown that it is, in fact, upon the bile pigment, that bradycardia depends.

It is at the moment impossible to form a definite opinion upon this question. While all recognize the hæmolysis as the remote cause of the jaundice, the majority of observers still cling to a point of view similar to that of Vaquez and Aubertin, which has been well summarized by Chalier. According to this the condition represents "a lesion of the blood of unknown cause terminating in destruction of the red blood corpuscles, in secondary splenic hyperplasia with the formation of an excess of iron-containing pigment and an overproduction of bile by the liver as a result of the superabundance of pigment to transform, and, consecutively jaundice." In their own words (Vaquez and Aubertin), " . . . . if the primary cause of hæmolytic jaundice is in an alteration of the blood, its immediate cause is without doubt an increased functional activity of the liver cell: there may exist, indeed, a biliary over-activity of the liver just as there exists a glycogenic over-activity of the liver, and hæmolytic icterus would then be an icterus through hepatic over-activity (*'ictère par hyper-hépatie'*)." Their idea as to the manner in which the bile pigment enters the blood is doubtless similar to that expressed by Leuret, "With the blood pigment modified by the spleen the hepatic cell proceeds to produce an excess of bilirubin to a degree such that in certain cases it overflows and secretes bile at both poles: whence hepatogenous icterus"—essentially the idea of Minkowski. The question must be regarded as still open, and there is much that would attract one to the hæmatogenous hypothesis of Widal, the argument in favor of this point of view being set forth strongly in the thesis of Troisier.

3. As to the third question, the primary cause of the corpuscular fragility, a positive answer cannot be given.

In congenital hæmolytic jaundice it has generally been assumed that the fragility of the red blood corpuscles is an inherited defect. The red cell, it might be fancied, has here failed to acquire those powers of resistance which are ordinarily gained in the first days of extra-uterine life, retaining permanently its original fragility. In the acquired forms of the disease the question is, however, by no means so simple. Widal, Abrami and Brulé, by intra-peritoneal injections of toluylendiamin, have produced in animals a jaundice with clinical and pathological phenomena similar to those observed in hæmolytic jaundice in the human being. According to the dose, the process was more acute and severe, or slower and more gradual and persisting for a long period after the last injection of the poison. No hæmolytic properties could be found in the serum. On the other hand the red blood corpuscles showed a markedly diminished resistance to hypotonic saline solutions as well as a granulation on vital staining, while evidences of increased marrow activity were striking. The urine in some of these cases, however, contained bile pigment. Obstructive jaundice in animals results neither in anæmia, granular corpuscles, nor increased fragility. Indeed, the resistance of the red blood corpuscles is always normal or increased. Here, then, is a similar phenomenon produced primarily by a soluble toxic substance, and while in many instances in the human being, no such cause is apparent, in other cases, such as those occurring in malaria, syphilis and uncinariasis, the primary action of some circulating toxic substance would appear to be certain. It may be, as suggested by Widal, that the marrow, constantly called upon, ends by producing corpuscles less resistant than the normal. But under such circumstances we must fancy that some poisons have acted primarily on blood or marrow. What these may be we know not. The fever associated with paroxysmal aggravations in some cases of acquired hæmolytic jaundice is suggestive of an infection.

It is possible, then, that the corpuscular fragility as well as the granular corpuscles, the main stigmata of the syndrome, may sometimes be secondary to the action of some circulating toxic substance or substances.

Treatment.—Various essays have been made in the treatment of both congenital and acquired hæmolytic jaundice. Widal and his pupils have shown clearly that the persistent administration of iron is the one method from which good

results may be obtained. In the severe acquired forms rest in bed and the other adjuvants suitable for the treatment of any grave anæmia should be adopted. In congenital hæmolytic jaundice recovery is unknown, but a temporary improvement in the anæmia may be obtained by persistent treatment with iron. In acquired hæmolytic jaundice long continued treatment may result in apparent, perhaps, indeed, in complete recovery (Widal, Abrami and Brulé). This is a very important fact when one reflects upon the futility of treatment with iron in Addisonian anæmia, a malady which may so closely resemble this syndrome.

* * * * *

The studies, then, of the last several years have brought out a fairly definite clinical syndrome, that of acholuric jaundice associated with splenomegaly and fragility of the red blood corpuscles. In its purest form this group of symptoms is manifested in a sharply defined disease picture, congenital, often familial splenomegalic jaundice. It is probable that many of Gilbert's cases of chronic simple jaundice with splenomegaly as well as of Hayem's infectious splenomegalic jaundice are examples of the disease.

A similar condition is, however, not infrequently met with in adult life. In these so-called acquired cases the symptoms are usually considerably more acute and severe than in the congenital malady.

The syndrome has, moreover, been found in a variety of other instances of non-obstructive jaundice associated with various infections or poisons.

What the essential primary element in these cases may be is not at present clear.

Most important for the moment is the recognition of those apparently idiopathic examples of acquired hæmolytic jaundice simulating pernicious anæmia, cholelithiasis, the so-called splenic anæmias, or, indeed, *icterus gravis*—most important because of the fact that the recognition and persistent treatment of some of these cases with iron may bring about a great improvement, and, perhaps, a permanent recovery.

The recognition of this syndrome has opened up again, and in an interesting manner, the question as to the possibility of a purely hæmatogenous jaundice.

The methods of studying the corpuscular resistance necessary for the diagnosis of such cases are, of course, too delicate for use by the busy practitioner, but they may be carried out easily in any well-equipped laboratory. One may hope that a re-investigation of some of the many instances of non-obstructive jaundice by means of these methods of study may help to shed further light upon an interesting field of medicine.

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WIDAL, F., et ABRAMI, P.
Types divers d'ictères hémolytiques non-congénitaux avec anémie. Recherche de la résistance globulaire par le procédé des hématies déplasmatisées. Tribune méd., Par., 1907, n. s., xxxix, 711.

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Les ictères d'origine hémolytique. Arch. d. mal. du cœur (etc.), Par., 1908, i, 193.
Auto-agglutination des hématies dans l'ictère hémolytique acquis. Compt. rend. Soc. de biol., Par., 1908, lxiv, 655-657.
Rétrocession des symptomes cliniques et des troubles hématiques au cours des ictères hémolytiques acquis. Bull. et mém. Soc. méd. d. hôp. de Par., 1909, 3. s., xxviii, 73-85.

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Ictère hémolytique développé au cours d'une anémie post hémorrhagique. Bull. et mèm. Soc. méd. d. hôp. de Par., 1908, 3. s., xxv, 468-474.
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WIDAL, F., and BÉNARD.
Biligénie hémolytique localisée à la peau sur de larges plaques d'erythème noueux sans extravasation sanguine. Compt. rend. Soc. de biol., Par., 1909, lxvi, 950.

WILSON, C.
Some cases showing hereditary enlargement of the spleen. Trans. Clin. Soc., Lond., 1890, xxiii, 162.

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Sequel to some cases showing hereditary enlargement of the spleen. Trans. Clin. Soc., Lond., 1893, xxvi, 163-171.

NOTES ON NEW BOOKS.

Dispensing Made Easy. By WM. G. SUTHERLAND, M. B., revised by F. J. WARWICK, M. B. (*Bristol: John Wright & Sons, 1910.*)

This little work contains a great deal of information especially valuable to the physician who does his own dispensing and to the pharmacist of a hospital or dispensary. There are directions for convenient ways of preparing many solutions and combinations of drugs. A number of formulas are given, many of which are taken from the pharmacopeias of the London hospitals. The book contains many practical points, and for the young practitioner it should prove a useful aid in mastering many of the practical details of prescribing.

Nurses' Handbook of Drugs and Solutions. By JULIA C. STIMSON, R. N., Superintendent of Nurses Harlem Hospital, of Bellevue and Allied Hospitals, New York City. Price $1.00. (*Boston: Whitcomb & Barrows, 1910.*)

It is very difficult to write a good textbook for nurses, and this one should, it seems to us, be merely used as a reference book, like a quiz compend. Too much has been crowded into it, and certain sections should either be omitted, or given in greater detain (*e. g.*, Part V, on Antitoxins, Vaccines, and Sera, with their uses). Such a sentence as the following will not be easily grasped by pupil nurses: "The only real success in securing pro-

tection against, and in the cure of diseases produced by micro-organisms, is now known to be based upon the artificial direction of the body's own immunizing ability, by means of removing obstacles to its action, of furnishing the appropriate stimulus when such is lacking, or by the addition to the blood stream of specific substances, which the body itself produces, but not in sufficient quantity to be effective in the production of a state of immunity against the infection under which it is struggling" (p. 68). Some of the "Rules for Solutions" are not expressed as clearly as might be, and in some places the metric system is used, and in others the apothecaries'. The value for nurses of such prescriptions as are given under "Common Formulæ" is problematic, to say the least.

Dawn of the Fourth Era in Surgery and Other Short Articles Previously Published. By ROBERT T. MORRIS, A. M., M. D., etc.

The author's many friends and admirers, as well as other students of surgery, will be pleased to have this collection of his papers in a neat and attractive form. Naturally all will not agree with Dr. Morris' dicta on certain surgical points, but his views deserve consideration, and an hour can be well spent rereading these articles, which deal with the use of the rubber glove, the appendix, the gall bladder, rapidity of operation, etc.

Principles of Therapeutics. By A. MANQUAT, National Correspondent to the Académie de Médicine. Translated by M. SINBAD GABRIEL, M. D. Price, $3.00. (*New York and London: D. Appleton & Co., 1910.*)

In this book the author discusses the general principles that underlie the giving of medicines, and the use of other therapeutic agents. It is dedicated to "young physicians," and "every line of it is devoted to *practice*, with the double object of being useful and doing no harm." It is divided into the following twelve chapters: I. Views of the Various Manners of Conceiving Therapeutics; II. The Forms of Therapeutic Action; III. Of the Action of Medicines; IV. Doses; V. Medicinal Opportunity; VI. Primum Non Nocere! VII. The Elements of Therapeutic Individualization; VIII. Influence of Environment on Therapeutic Results; IX. Variations of Therapeutic Activity Inherent in Medicines; X. Non-medicinal Therapeutic Actions; XI. Method in Therapeutics, and XII. Division of Therapeutic Agents. Much good advice is given, but it is not always presented in the happiest form; the author's style is not so lucid as that of many French writers, but those who have time to read this rather diffuse work will benefit themselves. Such clumsy and un-English words as "hyposthenizants," "hyposthenizing," "thermality," "nosocratic," "stomachal" and others mar the text, and the translation of many of the sentences is too literal and awkward. The definition of disease (p. 58) as "*the disturbance of the habitual organic equilibrium by the fact of an abnormal force acting with sufficient intensity to modify the fixity of its reactions, the habitual play of its functions and at times its structure and chemical composition, thus giving rise to disorders which persist until the accomplishment by this living matter of elimination or destruction of the modifying cause or else its own adaptation to the presence of the disturbing force*," may be intelligible in French, but is not readily comprehensible as it stands. "Nutritive movement" (p. 147) for digestion is not happy. In spite, however, of these defects in its English form, the book has value.

An Anatomical and Surgical Study of Fractures of the Lower End of the Humerus. By ASTLEY PASTON COOPER ASHHURST, A. B., M. D., etc. The Samuel D. Gross Prize Essay of the Philadelphia Academy of Surgery, 1910. (*Philadelphia and New York: Lea & Febiger, 1910.*)

Illustrated by case histories and excellent photographs and radiographs, this is a valuable monograph, one which every surgeon who sees many fractures will find helpful. The understanding of these fractures has been made clearer by Dr. Ashhurst's experimental and anatomical work. That the study is thorough is shown by the contents which include Introduction, Anatomy, Development of the Lower Epiphysis of the Humerus, Classification, Pathogenesis, Examination of the Patients, Supracondylar Fractures, Transverse, Diacondylar Fractures, Fractures of the External Condyle, Fractures of the Epitrochlea, Epiphyseal Separations, Fractures of the Internal Condyle, Intercondylar Fractures, Complications, Dressing the Elbow in Hyperflexion, Results, and Clinical Histories. The winning of the Samuel D. Gross Prize marks the distinction of this piece of work.

An Introduction to Surgery. By RUTHERFORD MORISON, M. A., M. B., F. R. C. S., Edin. and Eng., etc. Illustrated. Price, 8/6. (*Bristol: John Wright & Sons, Ltd. London: Simpkin, Marshall, Hamilton, Kent & Co., Ltd., 1910.*)

This work of about 150 pages is divided into ten chapters as follows: (1) Inflammation, (2) Bacteria, (3) Ulcers, (4) Gangrene, (5) Syphilis, Tubercle, and Malignant Disease, (6) Hæmophilia, (7) Wounds, (8) Abdominal and Pelvic Viscera, (9) Indications for Operation, (10) X-rays. It is difficult to understand for whom such a work is intended. Much of the teaching is puerile—it is like a book written in words of one syllable. Students who are not able to grasp more in an Introduction to Surgery, should not begin to study surgery. One poor paragraph on "Leucocytosis," and less than two pages on "Gonorrhœa" should not be considered as proper education to any class of students at any time in their career. Such a book is not really helpful to anyone. It is much too diagrammatic and epigrammatic.

Anæmia. By DR. P. EHRLICH and DR. A. LAZARUS. Part 1. Volume 1. Normal and Pathological Histology of the Blood. Second Edition. (Enlarged and to a great extent rewritten). By DR. A. LAZARUS and DR. O. NAEGELI. Translated for the German by H. W. ARMIT, M. R. C. S., L. R. C. P. (London). Illustrated. Price, $4.00. (*New York: Rebman Company, 1910.*)

The new edition of this well-known work will be welcome to all hæmatologists and clinicians. Ehrlich's studies of the blood are fundamental, and every student of this branch of medicine must be acquainted with them. This translation will, therefore, be of great help to those who are unable to read the original book in German. It is divided into four chapters. Chapter 1, Introduction; Definition—Clinical Methods of the Examination of Blood; and Chapter II, The Morphology of the Blood, are by Dr. Lazarus; Chapter III, The White Blood Corpuscles, by Dr. Naegeli; and Chapter IV, The Blood Platelets: The Hæmoconia, by Dr. Lazarus.

Applied Anatomy. The Construction of the Human Body Considered in Relation to Its Functions, Diseases and Injuries. By GWILYM G. DAVIS, M. D., Associate Professor of Applied Anatomy, University of Pennsylvania, etc. With 630 illustrations, mostly from original dissections and many in color, by Erwin F. Faber. (*Philadelphia and London: J. B. Lippincott Company.*)

Any thorough work which will aid the medical student to overcome the feeling that anatomy is a dull, dry subject, and has little practical relation to medicine, is welcome, and he who, along with his Gray, will read his Davis, will find that, after all, human anatomy is a living subject, and will be helped through many a tedious hour. The aim of the author "is to show the relation of structure to function" in both normal and pathological conditions, and with a clear text and abundance of illustrations, he has produced a really valuable book, which can be said of very few

modern medical works. The book is intended not alone for students, but surgeons and physicians will often find occasion to turn to its pages for information or the solution of some difficult problem. It is well arranged, and satisfactory in every way, except for its weight, excusable only by the handsome paper used.

Clinical Pathology in Practice, with a Short Account of Vaccine Therapy. By THOMAS J. HORDER, M. D., R. R. C. P., etc. Price, $3.00. (*London: Henry Frowde* and *Hodder & Stoughton, 1910.*) Oxford Medical Publications.

"The aim of this book is to present the practitioner with a brief survey of the scope and usefulness of modern pathological methods as applied to the diagnosis and treatment of disease. It is not intended to serve as a laboratory text-book . . . ." Such is the limitation of the book that many another laboratory text-book along these same lines is more useful to the student, since the practice of clinical pathology should go hand in hand with the theory of its use. After three preliminary chapters (Introductory, The Collection of Materials, Blood Culture) the author takes up The Histological Examination of the Blood, The Sputum, Pleural, Lung, Lumbar and Joint Puncture, Infective Conditions of the Nose, Mouth, Throat, and Urinary Tracts, Examination of the Fæces, the Diagnosis of Tuberculosis and Its Specific Treatment, Certain Specific Serum Tests and Their Value in Diagnosis, Fever without Other Physical Signs, and Vaccine Therapy. Simply and only as an introduction to the further study of these subjects can this book serve a purpose, and that rather inadequately.

A Manual of Nursing. By MARGARET FRANCES DONAHOE, formerly Superintendent of Nurses and Principal of Training School, Philadelphia General Hospital. Illustrated. (*New York and London: D. Appleton & Co., 1910.*)

This "Manual" covers all nursing and, therefore, is more complete than some of the treatises on this subject. On the whole, it is satisfactory, but it lacks distinction. The difference between a primary text-book on medicine and a treatise on nursing is not kept clearly in mind by the authoress, and this detracts from the value of the book, for some of her remarks in the chapter on the nursing of contagious diseases are not always correct. Throughout the work there are statements which need revision, but there are few errors of real consequence, and nurses will not be led far astray in reading this book, though they could spend their time better on some others.

International Clinics. Edited by HENRY W. CATTELL, A. M., M. D., with collaborators. Vol. IV. Twentieth Series, 1910. (*Philadelphia and London: J. B. Lippincott Company.*)

This volume opens with a timely article on "606" by the editor. It is important that the value and use of this new remedy should be thoroughly understood by the profession, and this article will be of material aid. Dr. J. J. Walsh has written another one of his entertaining and instructive historical papers on the "Physicians' Fees Down the Ages," and there are numerous other clinics on "Diagnosis and Treatment," "Medicine," "Surgery," "Neurology," "Pathology," "Ophthalmology," "State Medicine," and "Postgraduate Course," which will please and satisfy a variety of readers.

Studies in Invalid Occupation. A Manual for Nurses and Attendants. By SUSAN C. TRACY. Price, $1.50. (*Boston: Whitcomb & Barrows, 1910.*)

This is an excellent and most helpful work for the classes to whom it is addressed. The descriptions of objects to be made by the patients are clear, and there are a number of photographs and drawings which are also useful. To keep the hands of invalids with mental troubles of one sort and another, occupied is one of the most important means of curing them, and in any case, of preventing their mental condition becoming worse. Manual exercises of all kinds are an excellent means of keeping the minds of normal people healthy, and are still more important for the abnormal, and as an aid to all who care for those with mental disturbances this book can be heartily commended. Few attendants have sufficient imagination or knowledge to get on without a guide of this sort, and the majority will be glad of the assistance to be found in these "Studies."

A System of Syphilis in Six Volumes. Edited by D'ARCY POWER, M. B., Oxon., F. R. C. S., and J. KEOGH MURPHY, M. D., F. R. C. S. With an introduction by JONATHAN HUTCHINSON, F. R. S. Vol. II. (*London: Henry Frowde and Hodder & Stoughton, 1908.*) Oxford Medical Publication.

The editor-in-chief, Dr. D'Arcy Power, opens this volume with an interesting and able paper on the "Surgery of Syphilis," and he is followed by Col. F. J. Lambkin, who contributes two noteworthy papers on "The Treatment of Syphilis," and "An Outbreak of Syphilis in a Virgin Soil." The final chapter on "Syphilis in Obstetrics" is well handled by Dr. William J. Gow. Since the appearance of this volume two years ago the new method of treating syphilis with "606" has been discovered, but this remedy will not altogether drive out of use or supplant the older ones, so that Col. Lambkin's paper on treatment is still well worth reading and studying. There is no doubt that for all students of syphilis this is a most important system, and each volume contains papers of exceptional value. Such experiences as Col. Lambkin had with this disease in Uganda are exceedingly rare and of the greatest interest. The volume is illustrated with some beautiful color reproductions.

American Practice of Surgery. A Complete System of the Science and Art of Surgery. By Representative Surgeons of the United States and Canada. Editors: JOSEPH D. BRYANT, M. D., LL. D.; ALFRED H. BUCK, M. D. Complete in eight volumes, profusely illustrated. Vol. VI. (*New York: William Wood & Co., 1909.*)

The surgeons, who contribute articles to this volume, are: Armstrong, Elder and Shepherd, of Montreal; Balch, Cabot, Graves and Mosher, of Boston; Carson and Mudd, of St. Louis; Bloodgood, of Baltimore, and Turner, of Philadelphia. Unless one turns to the individual articles there is no means of quickly finding the respective authors, whose names might have readily been placed after the subject headings under "Contents." Bloodgood's paper on the "Surgical Diseases of the Jaws" is separated from other papers on the surgery of the face and throat by a number of papers on the surgery of the female and male genitals. These are minor defects, but in a well-arranged system they would not occur. The very completeness of this sytem leads to redundancy of material. The volume opens with a paper on Prosthesis in its Relation to Surgery of the Face, Mouth, Jaws and Nasal and Laryngeal Cavities, followed in sequence by chapters on Surgical Diseases and Wounds of the Nasal Cavities and Accessory Sinuses; Surgical Diseases and Wounds of the Mouth, Tongue, and Salivary Glands; Surgical Diseases and Wounds of the Neck; Surgical Diseases and Wounds of the Thyroid and Thymus; Surgery of the Thorax and Spinal Column; Surgical Diseases and Wounds of the Female Breast; Surgical Diseases and Wounds of the External Genitals and Vagina of the Female; Surgical Diseases and Wounds of the Male Genital Organs; Chancroid; Gonorrhœal Uret[illegible], and Surgical Diseases and Wounds of the Jaws. Thus these articles take up 900 pages and the volume is so heavy as to be unwieldy. There are but few references, which seems rather a defect in a classical work of this nature, but the question of mul-

tiple references is a debated one. Many of the drawings and photographs are excellent, but the colored plates are not good. The articles, on the whole, cover the ground well, and the surgeon in need of this system will find it a useful book. This volume may be said to well uphold the repute already gained by American and Canadian surgeons, and while there is no paper of exceptional merit in this volume, the general average of excellence is high.

Hydrotherapy. A Work on Hydrotherapy in General, Its Application to Special Affections, The Technic or Processes Employed and the Use of Waters Internally. By GUY HINSDALE, A. M., M. D., etc. Illustrated. Price, $3.50. (*Philadelphia and London: W. B. Saunders Company, 1910.*)

A few years ago the number of text-books on this subject was limited, but they are now constantly increasing in numbers, and there is no longer any reason why the general practitioner should not have a clear idea of the uses and value of water applied both internally and externally. The best part of most of these text-books is the description of the technic in giving the different forms of baths and sprays. The authors have a tendency, it seems to us, to exaggerate the value of water in many affections, but it must be said that those who do not use hydrotherapy freely do not recognize its many values. This work is a smaller one than Kellogg's, and sufficient for the use of the ordinary practitioner. The chapter on the use of baths in typhoid fever, where correct use of water is so important, is, however, most unsatisfactory, it is far too brief, and the author should have given a fuller account of their action, and when they should and should not be given.

It is a pity to add to our medical terms such words as "Crounotherapy" and "Crenology," which are really not needed, and the same figure with slightly different description is given on pages 73 and 245.

The Mental Symptoms of Brain Diseases—An Aid to the Surgical Treatment of Insanity, Due to Injury, Hæmorrhage, Tumors and Other Circumscribed Lesions of the Brain. By BERNARD HOLLANDER, M. D. With Preface by Dr. Jul. Morel. Price $2. (*New York: Rebman Company, 1910.*)

In this work the author has classified a large number of cases taken from the literature under lesions of the different lobes depending on the nature of the symptoms shown. Under lesions of the frontal lobes he groups cases where the higher intellectual operations or the centers of perception and special memories or the higher human sentiments seem to be most affected. Cases of melancholia are grouped under lesions of the parietal lobes; and others of violent and homicidal mania fall under lesions of the temporal lobes, and so on. Such a classification as all neurologists know cannot be exact, for symptoms are not always clear cut, but one group shades into another, and an exact diagnosis of the site of the lesion cannot be made. The book, if used with thought, may, however, be helpful as a guide to students in their earlier studies of brain lesions.

BOOKS RECEIVED.

A Text-Book of Bacteriology. A Practical Treatise for Students and Practitioners of Medicine. By Philip Hanson Hiss, Jr., M. D., and Hans Zinsser, M. D. With one hundred and fifty-six illustrations in the text, some of which are colored. 1910. 8vo. 745 pages. D. Appleton and Company, New York and London.

Diseases of Infants and Children. By Edmund Cautley, M. D., Cantab., F. R. C. P. Lond. 1910. 8vo. 1042 pages. Paul B. Hoeber, New York.

The Sexual Disabilities of Man and Their Treatment. By Arthur Cooper. Second edition, revised and enlarged. 1910. 16mo. 204 pages. Paul B. Hoeber, New York.

Urinary Surgery. A Review. By Frank Kidd, M. D., B. C. (Cantab.), F. R. C. S. 1910. 8°. 429 pages. Longmans, Green and Company, London, New York, Bombay and Culcutta.

Phases of Evolution and Heredity. By David Berry Hart, M. D., F. R. C. P. E. 12mo. 259 pages. Rebman Company, New York.

The Principles and Practice of Medicine. By William Osler, M. D., F. R. S. Seventh edition. Translated by Philip B. Cousland, M. B., C. M., Edin. 1910. 8vo. Publication Committee, China Medical Missionary Association, Shanghai.

An Anatomical and Surgical Study of Fractures of the Lower End of the Humerus. By Astley Paston Cooper Ashhurst, A. B., M. D. The Samuel D. Gross Prize Essay of the Philadelphia Academy of Surgery, 1910. 8vo. 163 pages. Lea & Febiger, Philadelphia and New York.

A Manual of Nursing. By Margaret Frances Donahoe. Illustrated. 1910. 12mo. 489 pages. D. Appleton and Company, New York and London.

Report of the Surgeon-General, United States Army, to the Secretary of War, 1910. Annual Reports, War Department. Fiscal year ended June 30, 1910. 8vo. 223 pages. Government Printing Office, Washington.

Recherches d'Anatomie Chirurgicale sur les Artères de l'Abdomen; Le Trona Coeliacque. Par Pierre Descomps. 1910. 4°. 205 pages. G. Steinheil, Paris.

Eléments d'Anatomie Pathologique. Par L. Bériel. Avec 232 figures dessinées par le l'auteur. 8vo. 563 pages. G. Steinheil, Paris.

Urgent Surgery. By Félix Lejars. Translated from the sixth French edition by William S. Dickie, F. R. C. S. With 20 full-page plates and 994 illustrations, of which 602 are drawn by Dr. E. Daleine and A. Leuba, and 217 are from original photographs. Vol. II. The Genito-Urinary Organs—The Rectum and Anus—the Strangulated Hernias—the Extremities. 1910. 4to. 580 pages. William Wood and Company, New York.

The Mental Symptoms of Brain Disease. An Aid to the Surgical Treatment of Insanity, due to Injury, Hæmorrhage, Tumors and other Circumscribed Lesions of the Brain. By Bernard Hollander, M. D. With preface by Dr. Jul. Morel. [1910.] 12mo. 237 pages. Rebman Company, New York.

The Modern Treatment of Alcoholism and Drug Narcotism. By C. A. McBride, M. D., L. R. C. P. & S. (Edin.) [1910]. 12mo. 376 pages. Rebman Company, New York.

Hints for the General Practitioner in Rhinology and Laryngology. By Dr. Johann Fein. Translated by J. Bowring Horgan, M. B., B. Ch. With forty figures in the text and two photographic plates. [1910.] 12mo. 223 pages. Rebman Company, New York.

Anæmia. By Geh. Obermedizinalrat Professor Dr. P. Ehrlich and Dr. A. Lazarus. Volume 1. Part 1. Normal and Pathological Histology of the Blood. Second edition (enlarged and to a great extent rewritten), by Dr. A. Lazarus and Dr. O. Naegeli. Translated from the German by H. W. Armit, M. R. C. S., L. R. C. P. (London). With 5 illustrations in the text and 5 colored plates. 1910. 8vo. 218 pages. Rebman Company, New York.

Diagnosis and Treatment of Diseases of Women. By Harry Sturgeon Crossen, M. D. Second edition, revised and enlarged. With seven hundred and forty-four engravings. 1910. 8vo. 1025 pages. C. V. Mosby Company, St. Louis.

Dispensing Made Easy. With Numerous Formulæ, and Practical Hints to Secure Simplicity, Rapidity and Economy. By Wm. G. Sutherland, M. B. Aberd. Fourth edition, revised by F. J. Warwick, B. A., M. B. Cantab., M. R. C. S., L. S. A. 1910. 16°. 102 pages. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent and Co., Ltd., London.

The Diseases of China, Including Formosa and Korea. By W. Hamilton Jefferys, A. M., M. D., Univ. of Pennsylvania, and James L. Maxwell, M. D. London. With 5 colored plates, 11 nosogeographical plates, and 360 illustrations in the text. 1910. 8vo. 716 pages. P. Blakiston's Son & Co., Philadelphia.

Modern Treatment. The Management of Disease with Medicinal and Non-Medicinal Remedies. In Contributions by American and Foreign Authorities. Edited by Hobart Amory Hare, M. D. Assisted by H. R. M. Landis, M. D. In Two Volumes. Volume I. Illustrated. 1910. 8vo. 930 pages. Lea & Febiger, Philadelphia and New York.

The Racial Anatomy of the Philippine Islanders. Introducing New Methods of Anthropology and Showing their Application to the Filipinos with a Classification of Human Ears and a Scheme for the Heredity of Anatomical Characters in Man. By Robert Bennett Bean, B. S., M. D. With nineteen illustrations reproduced from original photographs. Seven figures. 1910. 8vo. 236 pages. J. B. Lippincott Company, Philadelphia and London.

Progressive Medicine. A Quarterly Digest of Advances, Discoveries and Improvements in the Medical and Surgical Sciences. Edited by Hobart Amory Hare, M. D., assisted by Leighton F. Appleman, M. D. Volume IV. December, 1910. 8vo. 360 pages. Lea & Febiger, Philadelphia and New York.

Scientific Memoirs. New Series, No. 38. By Officers of the Medical and Sanitary Departments of the Government of India. *Preliminary Report on the Killing of Rats and Rat Fleas by Hydrocyanic Acid Gas.* By Captain W. D. H. Stevenson, M. B., I. M. S. 1910. Fol. 28 pages. Superintendent Government Printing, Calcutta, India.

An Introduction to Surgery. By Rutherford Morison, M. A., M. B., F. R. C. S. Edin and Eng. With 146 illustrations in the text, and 5 colored plates. 1910. 4to. John Wright & Sons, Ltd., Bristol; Simpkin, Marshall, Hamilton, Kent & Co., Ltd., London.

Practical Bacteriology, Blood Work and Animal Parasitology. Including Bacteriological Keys, Zoological Tables and Explanatory Clinical Notes. By E. R. Stitt, A. B., Ph. G., M. D. Second edition, revised and enlarged with 91 illustrations. 1910. 12°. 345 pages. P. Blakiston's Son & Co., Philadelphia.

International Clinics. A Quarterly of Illustrated Clinical Lectures and Especially Prepared Original Articles. Edited by Henry W. Cattell, A. M., M. D. Volume IV. Twentieth Series, 1910. 8vo. 308 pages. J. B. Lippincott Company, Philadelphia.

Principles of Therapeutics. By A. Manquat. Translated by M. Simbad Gabriel, M. D. 1910. 8vo. 298 pages. D. Appleton and Company, New York and London.

Clinical Pathological in Practice. With a Short Account of Vaccine-Therapy. By Thomas J. Horder, B. Sc., M. D., F. R. C. P. 1910. 8vo. 216 pages. Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

Puerperal Infection. By Arnold W. W. Lea, M. D., B. S. (Lond.), B. Sc. (Manch.), F. R. C. S. (Eng.). 1910. 8vo. 384 pages. Oxford Medical Publications. Henry Frowde, London; Hodder & Stoughton, London.

Induced Cell-Reproduction and Cancer. The Isolation of the Chemical Causes of Normal and of Augmented, Asymmetrical Human Cell-Division. By Hugh Campbell Ross, M. R. C. S. (Eng.), L. R. C. P. (Lond.). Being the results of researches carried out by the author with the assistance of John Westray Cropper, M. B., M. Sc. (Liv.), M. R. C. S. (Eng.), L. R. C. P. (Lond.). With 129 illustrations. 1911. 8vo. 423 pages. P. Blakiston's Son & Co., Philadelphia.

Emanuel Swedenborg's Investigations in Natural Science and the Basis for His Statements Concerning the Functions of the Brain. By Martin Ramström. 1910. 4to. 59 pages. University of Upsala.

Studies in Invalid Occupation. A Manual for Nurses and Attendants. By Susan E. Tracy. 1910. 8vo. 175 pages. Whitcomb & Barrows, Boston.

Nurses Handbook of Drugs and Solutions. By Julia C. Stimson, R. N. 1910. 12°. 82 pages. Whitcomb & Barrows, Boston.

A Text-Book of General Bacteriology. By Edwin O. Jordan, Ph. D. Second edition, thoroughly revised. Fully illustrated. 1910. 8vo. 594 pages. W. B. Saunders Company, Philadelphia and London.

The Practice of Surgery. By James Gregory Mumford, M. D. With 682 illustrations. 1910. 8vo. 1015 pages. W. B. Saunders Company, Philadelphia and London.

Hydrotherapy. A Work on Hydrotherapy in General, its Application to Special Affections, the Technique or Processes Employed, and the Use of Waters Internally. By Guy Hinsdale, A. M., M. D. Illustrated. 1910. 8vo. 466 pages. W. B. Saunders Company, Philadelphia and London.

Treatise on Diseases of the Skin. By Henry W. Stelwagon, M. D., Ph. D. Sixth edition, thoroughly revised. With 289 illustrations in the text, and 34 full-page colored and half-tone plates. 1910. 8vo. 1195 pages. W. B. Saunders Company, Philadelphia and London.

Dawn of the Fourth Era in Surgery. And Other Short Articles Previously Published. By Robert T. Morris, A. M., M. D. 1910. 12°. 145 pages. W. B. Saunders Company, Philadelphia and London.

Transactions of the American Gynecological Society. Volume 35. For the year 1910. 8vo. 566 + LXII pages. Philadelphia.

Transactions of the Congress of American Physicians and Surgeons. Eighth Triennial Session held at Washington, D. C., May 3 and 4, 1910. 8vo. 456 pages. Published by the Congress, New Haven, Conn.

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